Czech Technical University in Prague

Faculty of Biomedical Engineering

Department of Biomedical technology

Doctoral Thesis

2019

Svitlana Strunina

Czech Technical University in Prague
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EXTRACORPOREAL CIRCULATORY SUPPORT IN THE THERAPY OF CARDIAC ARREST AND CARDIOGENIC SHOCK

Doctoral Thesis

Svitlana Strunina

Kladno, 2019

Ph.D. Programme: *Biomedical and clinical technology*
Branch of study: *Biomedical and clinical technology*

Supervisor: ***doc. Ing. Jiří Hozman, Ph.D.***
CoSupervisor: ***doc. MUDr. Petr Ošt'ádal, Ph.D.***
CoSupervisor: ***doc. MUDr. Jiří Kofránek, CSc.***

Hereby I declare that the doctoral thesis "Extracorporeal circulatory support in the therapy of cardiac arrest and cardiogenic shock" has been written by me in its entirety as the result of my own original research. I have acknowledged all the sources of information which have been used in the doctoral thesis in compliance with the Methodological Instruction No. 1/2009 - On maintaining ethical principles when working on a university final project.

26.06.2019

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Svitlana Strunina

Acknowledgments

My deep thanks belong to my whole big family and friends who have supported me along the way, encourage and helped me. I cannot list all the name here, but you are always on my mind. My special thanks go to my parents, my mother Larysa Dehtiarova and my father Oleksandr Strunin (sadly now deceased), for allowing me to realize my own potential, for their love and support they have provided me over the years.

I would like to express my sincere gratitude to my supervisor Jiří Hozman for his continuous support of my Ph.D. study and related research, for his patience and motivation. His guidance helped me in all the time of research and writing of this doctoral thesis.

I would like to express my gratitude to my co-supervisors Petr Ošťádal from the Cardiovascular Center, Na Homolce Hospital, and Jiří Kofránek from Institute of Pathological Physiology, Charles University in Prague for the opportunity to work on my Ph.D. thesis and for bringing me into the word of research, for sharing with me a lot of their experience and insights.

The work performed would not have been possible without all staffs of Electrophysiological Laboratory and The Laboratory of Biocybernetics and Computer Aided Teaching, First Faculty of Medicine, Charles University. They have been very professional, helpful and kind. Without their precious support, it would not be possible to conduct this research.

I wish to thank Natalia Maritz and Vitaliy Maksymenko from National Technical University of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute" and Peter Kneppo from Czech technical university in Prague who provided me an opportunity to join a team of the Faculty of Biomedical Engineering. I wish to thank Stephanie Krueger, Filip Strych, and Ibrahim Abou Khashabh from the National Library of Technology in Prague and Lenka Lhotská from Czech technical university in Prague for help and support. I wish to thank in special to Jan Tešný, without his support it would not be possible to finish this doctoral thesis.

This work was partially supported by the Grant Agency of the Czech Technical University in Prague, grant No. SGS17/112/OHK4/1T/17.

Abstract

Cardiogenic shock and cardiac arrest still have a poor prognosis with a high mortality rate. Extracorporeal membrane oxygenation is increasingly used for the treatment of cardiogenic shock; it is an indispensable therapy for the acute treatment of patients with cardiogenic shock and cardiac arrest. However, extracorporeal membrane oxygenation has a significant risk of complications. An important pitfall of extracorporeal membrane oxygenation, which can highly impair patient outcome, is inappropriate left ventricular unloading. A number of approaches have been suggested for dealing with left ventricular unloading during extracorporeal membrane oxygenation. Nevertheless, each of the currently existing methods requires further intervention; the nowadays methods can be the reason of additional complications such as bleeding, infection, and prolong recovery time of extracorporeal membrane oxygenation treated patients. The left ventricular decompression, during extracorporeal membrane oxygenation therapy, is associated with significant improvement of the left ventricular function. Therefore, the development of a mini-invasive method of left heart decompression is a significant issue in extracorporeal membrane oxygenation therapy. The purpose of this doctoral thesis is to develop an alternative method of left ventricular unloading or left ventricular overload reduction, which has the potential for reducing the invasiveness of left ventricular unloading during veno-arterial extracorporeal membrane oxygenation therapy, based on modeling, simulation, and experiments. Data of hemodynamic and cardiac performance parameters were obtained from porcine models of cardiogenic shock; some of these data were used for numerical modeling and numerical simulations in the Modelica modeling language (Modelica Association) in the Dymola (Dassault Systemes) modeling environment and using the components from Physiolibrary 2.3.1. The statistical analysis of obtained data from a porcine model of cardiogenic shock was conducted by using GraphPad Prism 5.0 software (GraphPad, USA) and R 3.5.3 software (The R Foundation, Vienna, Austria). The drafts of the double lumen arterial cannula for extracorporeal membrane oxygenation was created in AutoCAD software. An experimental study in a porcine model of cardiogenic shock confirmed the undesirable negative effects of veno-arterial extracorporeal membrane oxygenation on left ventricular performance parameters in a flow-dependent manner. The simulation study indicated that the double lumen arterial cannula cannula for veno-arterial extracorporeal membrane oxygenation with 10 Fr drainage lumen achieves reduction of left ventricular loading, and it takes into account human physiological features. With decreasing venous cannula size, the percentage of left ventricular loading during veno-arterial extracorporeal membrane oxygenation is decreased without an increase of double lumen arterial cannula size. An experimental study in a porcine model of cardiogenic shock confirms that with the application of double lumen arterial cannula instead of the standard arterial cannula during veno-arterial extracorporeal membrane oxygenation, there is a significant improvement in selected hemodynamic parameters. Among other things, biomedical engineering involves advising manufacturers of medical devices on promising improvements based on clinical experience, the application, and implementation of medical technologies to optimize the delivery of medical care. These aspects of biomedical engineering are realized in this doctoral thesis. The double lumen arterial cannula presents a promising solution and has the potential for reducing the invasiveness of left ventricular unloading during veno-arterial extracorporeal

membrane oxygenation therapy. It is intended that the double lumen arterial cannula will help to mitigate such extracorporeal membrane oxygenation complications as left ventricular overload; furthermore, eliminating the complications of current methods for left ventricular decompression, such as an additional source of bleeding, infection, and longer recovery time of extracorporeal membrane oxygenation treated patients.

Key words: cardiogenic shock, cardiac arrest, extracorporeal membrane oxygenation therapy, left ventricular overload, unloading, peripheral cannula, experimental study, modeling, simulation

Contents

1 Introduction

Cardiogenic shock (CS) and cardiac arrest (CA) still have an unfavorable prognosis with a high mortality rate despite numerous efforts in diagnosis and therapy [78]. Patient prognosis significantly depends on the time between CS or CA and the restoration of adequate end-organ perfusion [41]. Extracorporeal Life Support (ECLS) is an indispensable therapy for the acute treatment of patients with CS and CA [41, 120, 78]. The important advantages of ECLS are its relative ease of implantation and an immediate reversal of inadequate systemic perfusion [24].

Extracorporeal life support or membrane oxygenation support (ECMO) is a mechanical device that supports or replaces heart and/or lung functions. ECMO is accepted worldwide as a lifesaving treatment; this technology has been used for more than thirty years [85]. ECMO has been a standard treatment for respiratory failure in newborn infants and children for many years [85, 95]; nonetheless, this technology has been applied to adult respiratory and cardiac failure throughout the world.

ECMO can be used for days or weeks to support or replace lung and/or heart function, leading to recovery of failing organs; nevertheless, the impact of ECMO on left ventricular (LV) unloading is still debated. ECMO provides excellent support for circulation; however, the capacity of ECMO to effectively assist the heart, notably the LV, is limited [68].

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has been shown to provide some degree of LV unloading during short duration of ECMO therapy [18], but it is very important to provide an effective left heart decompression while increasing the duration of ECMO support [68, 122].

Poor LV decompression, during VA-ECMO therapy, frequently can lead to pulmonary edema, pulmonary hemorrhage; it may results in dilatation of the left heart, deterioration of heart performance, and reduced subendothelial perfusion leading to myocardial ischemia [120, 44, 38].

A number of approaches have been suggested for dealing with LV unloading. Each of the current methods for LV decompression during VA-ECMO, requires further intervention which increases the invasiveness of the method and thus does not respond to current trends in mini-invasive performance. Therefore, the development of a less-invasive method than the current existing methods, for left heart decompression is a significant area of investigation in ECMO therapy. In this doctoral thesis, the development of such an alternative method of LV unloading, which has the potential for reducing the invasiveness of LV unloading during VA-ECMO therapy is described. This doctoral thesis deals with using of a double lumen arterial cannula (DLAC) for VA-ECMO, as an alternative method for the reduction of left heart loading in ECMO treated patients, and the impact of DLAC on LV decompression during ECMO.

The doctoral thesis is composed of six chapters, each of them dealing with different aspects of ECMO in the therapy of CA and CS. Following an introductory chapter, Chapter 2 focuses on the current state of the VA-ECMO in the therapy of CA and CS. The chapter highlights ECMO therapy and hemodynamic and cardiac performance parameters in ECMO treated individuals with CA and CS. The chapter describes the pitfall of the VA-ECMO therapy as LV overload, provides an overview of the methods of LV unloading during ECMO therapy and deals with the peripheral cannulas applied in extracorporeal life circulatory support (ELCS). Chapter 3 focuses on the aim and objectives of the doctoral thesis. The main aim was to develop an alternative method of LV unloading or LV overload reduction, which has the potential for reducing the invasiveness of LV unloading during VA-ECMO therapy. Chapter 4 describes the material and methods, in other words, methodology and techniques for the collection the data and analysis of archived data. Chapter 5 outlines the results and discussion. This chapter deals with experimental study with porcine model of CS, further these data were used for modeling and simulation; describes a novel method to unload LV during VA-ECMO; explains the investigation of DLAC capacities for LV decompression during VA-ECMO therapy asses by mathematical modeling and simulation and analyze the

capability of a DLAC to unload LV during ECMO in porcine model of CS. Summary and future perspectives are drawn in Chapter 6. The main aim of the doctoral thesis has been reached. On the basis of the results of conducted studies, it can be concluded that DLAC presents a promising solution for LV unloading during VA-ECMO, and has the potential for reducing the invasiveness of LV unloading during VA-ECMO therapy. It is a novel method to mitigate negative sequelae of VA-ECMO.

2 State of the art

The purpose of this chapter is to describe ELCS, or ECMO technology, hemodynamic and cardiac performance parameters in ECMO treated individuals. Furthermore, this chapter also deals with the advantages and disadvantages of ECMO therapy, and it introduces the currently existing methods to prevent LV overload of patients on VA-ECMO. Lastly, the chapter describes the parameters and features of the available peripheral cannulas.

For the literature review, the following databases were used EBSCOhost Research Databases, IEEE Xplore, ScienceDirect, Scopus, SpringerLink, Wiley Online Library, Critical Care, and PubMed.

The following words and phrases were used to find the necessary information: ECMO; left ventricular decompression; cardiogenic shock; left ventricular rest; left ventricular unloading during VA-ECMO; prevention LV distensions during ECMO therapy; extracorporeal life support; prevention pulmonary edema during ECMO therapy; ECMO y connector decompression; cannula dimensions; cannula material; cannula position; complications; extracorporeal membrane oxygenation; surface coating.

2.1 Extracorporeal membrane oxygenation therapy

ECMO falls under the broader heading of extracorporeal life support [44]. ECMO is a technology allowing extended support with an acceptable rate of hemolysis and coagulation impairment. Modern ECMO devices are more and more compact and easy to use, and they are also optimized for transportation and to facilitate the implantation of the system wherever the emergency occurs [13].

ECMO leads to circulatory support with the opportunity to oxygenate the blood; it is a miniaturized and simplified form of cardiopulmonary bypass [78, 82]. The principle of ECMO is that an external artificial circulator draws a portion of blood outside of the body, through a cannula and tubing, and after oxygenation (increasing the oxygen level) and decarboxylation

(CO_2 removal) into a gas exchange device (oxygenator), the blood returns to the circulation via another tubing and cannula [25, 62, 61, 78, 82]. There are two types of ECMO: veno-venous extracorporeal membrane oxygenation (VV-ECMO) which is typically used for gas exchange failure (Figure 1), and VA-ECMO which is typically used for circulatory failure (Figure 2).

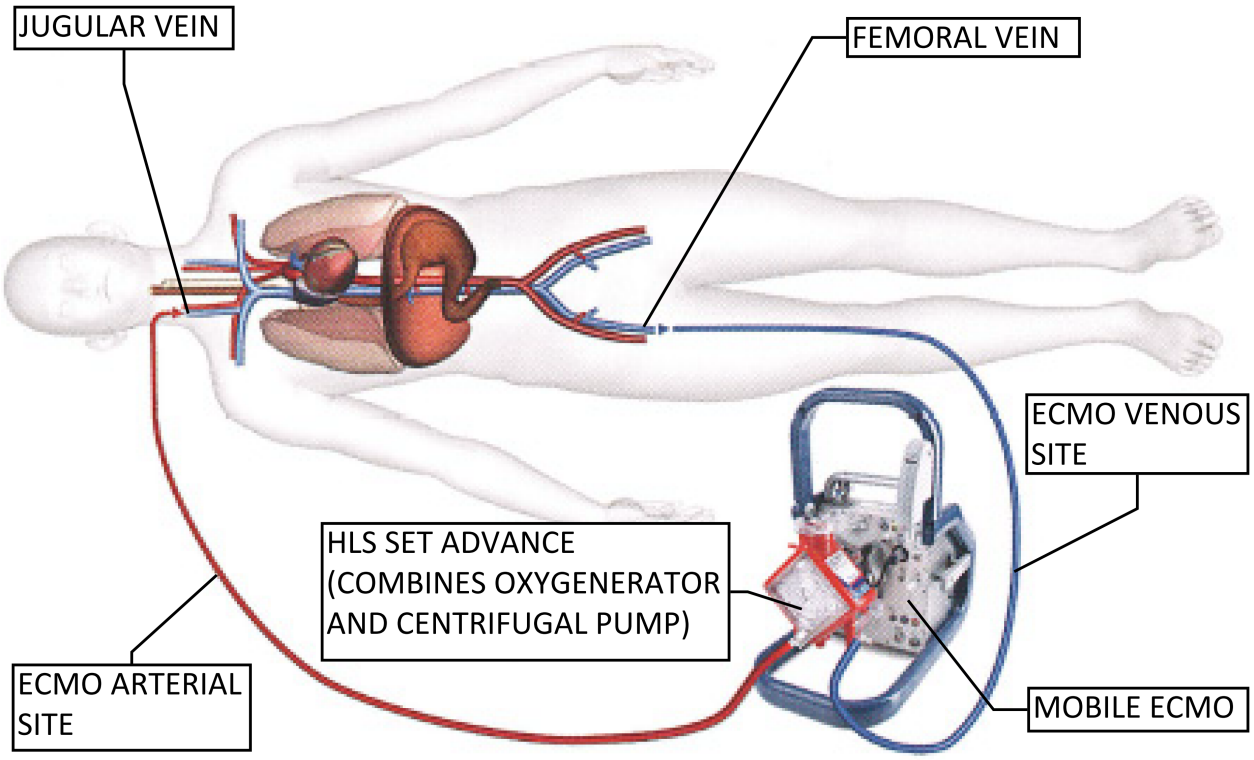


Figure 1: Peripheral veno-venous extracorporeal membrane oxygenation. Reprinted with permission from Maquet Czech Republic s.r.o.

This doctoral thesis deals with ECMO in veno-arterial configuration. ECMO in veno-arterial configuration provides right atrium-to-aorta circulatory support. The VA-ECMO circuit consists of a venous inflow cannula (Figure 3), an extracorporeal blood pump, an oxygenator, an arterial outflow cannula (Figure 3), and connecting tubes. In minimally invasive (ie, peripheral) settings, the inflow cannula is usually inserted percutaneously through the femoral or jugular vein into the right atrium. The deoxygenated venous blood is drawn from the right atrium and is pumped by a centrifugal pump (Figure 4) to the oxygenator (Figure 5)

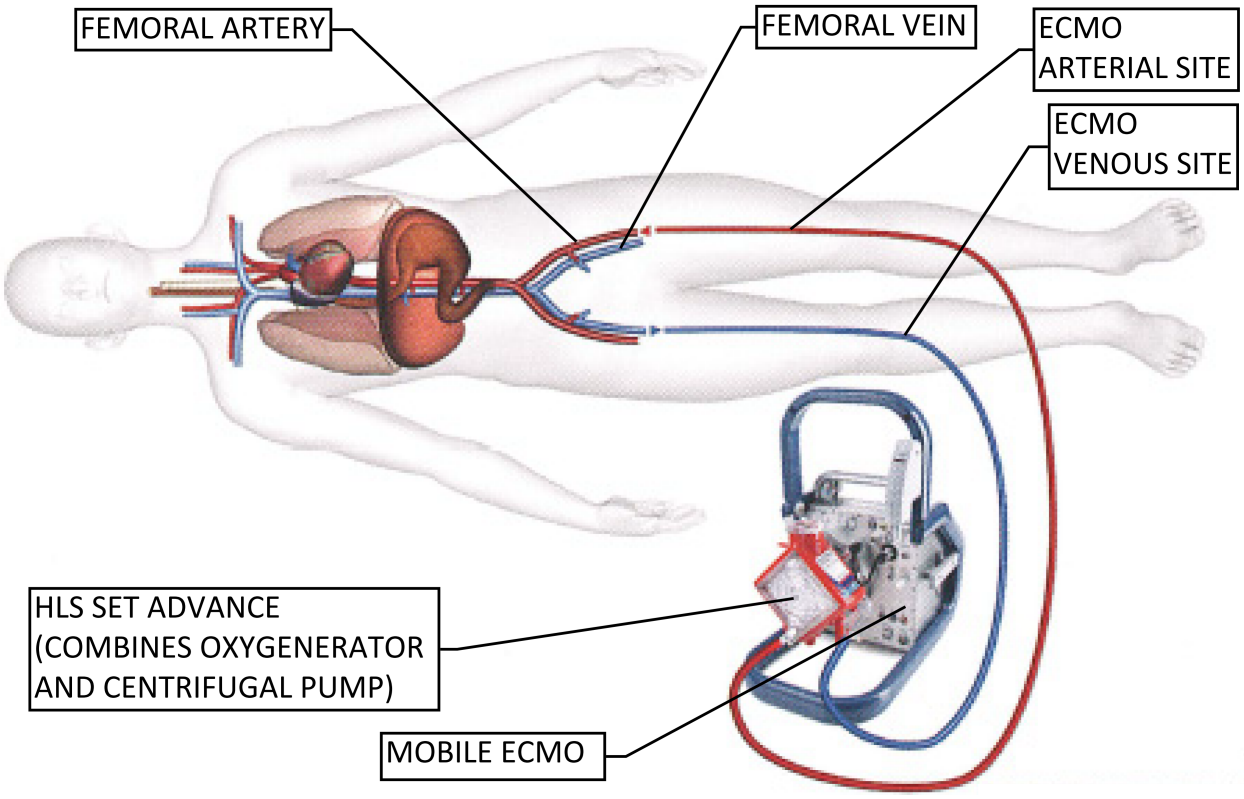


Figure 2: Peripheral veno-arterial extracorporeal membrane oxygenation. Reprinted with permission from Maquet Czech Republic s.r.o.

herein blood gases are exchanged. Nowadays ECMO pumps are centrifugal; they generate continuous or pulsatile flow. It was estimated that the electrocardiographic-synchronized pulsatile ECLS flow preserves LV function in comparison with standard continuous-flow ECLS in CS [86]. After oxygenation, blood is returned to the aorta via an arterial outflow cannula; it is usually inserted into the femoral artery, in peripheral settings.

A notable advantage of ECMO is that cannulation may be performed nearly everywhere; the system and all parts are transportable. ECMO mobility enables the medical team to use it during transport of patients (Figure 6) [78].

In general, ECMO can be used with different strategies. In patients with severe CS from myocarditis or myocardial infarction, mechanical support is commonly utilized in a bridge-to-recovery approach. During the resuscitation of patients, a bridge-to-decision strategy usually requires ECMO implantation, by the ECMO team, for further therapy [78]. ECMO provides

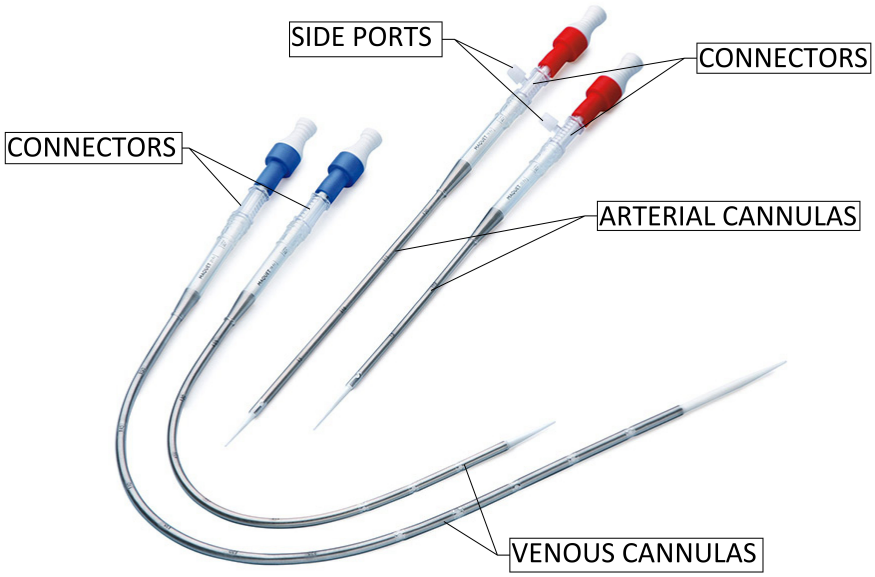


Figure 3: A venous inflow cannula (on the left) an arterial outflow cannula (on the right) for veno-venous and veno-arterial vessel access for ECMO support. Reprinted with permission from Maquet Czech Republic s.r.o.

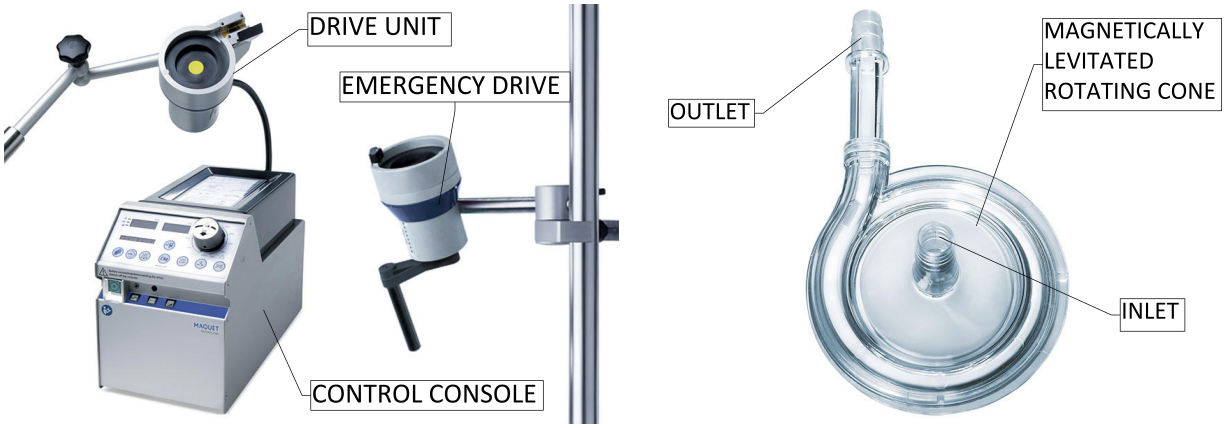


Figure 4: A centrifugal pump for extracorporeal membrane oxygenation support. Reprinted with permission from Maquet Czech Republic s.r.o.

excellent short-term circulation support [5]. Successful ECMO use has been reported in acute CS, acute decompensation of congestive heart failure, drug intoxication, accidental hypothermia, and cardiopulmonary resuscitation during CA [41, 85, 68, 122, 44, 62, 61, 34, 9, 107, 52, 50, 11]. Several case series reported the use of VA-ECMO as support for high-risk percutaneous coronary and valvular intervention [41, 10], arrhythmic storm, or

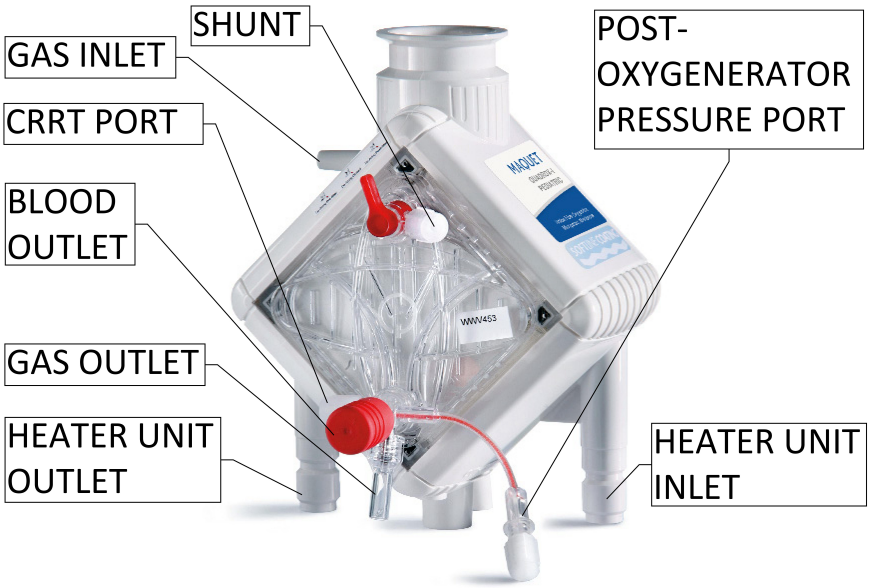


Figure 5: A oxygenator for extracorporeal membrane oxygenation support. CRRT - Continuous renal replacement therapy. Reprinted with permission from Maquet Czech Republic s.r.o.

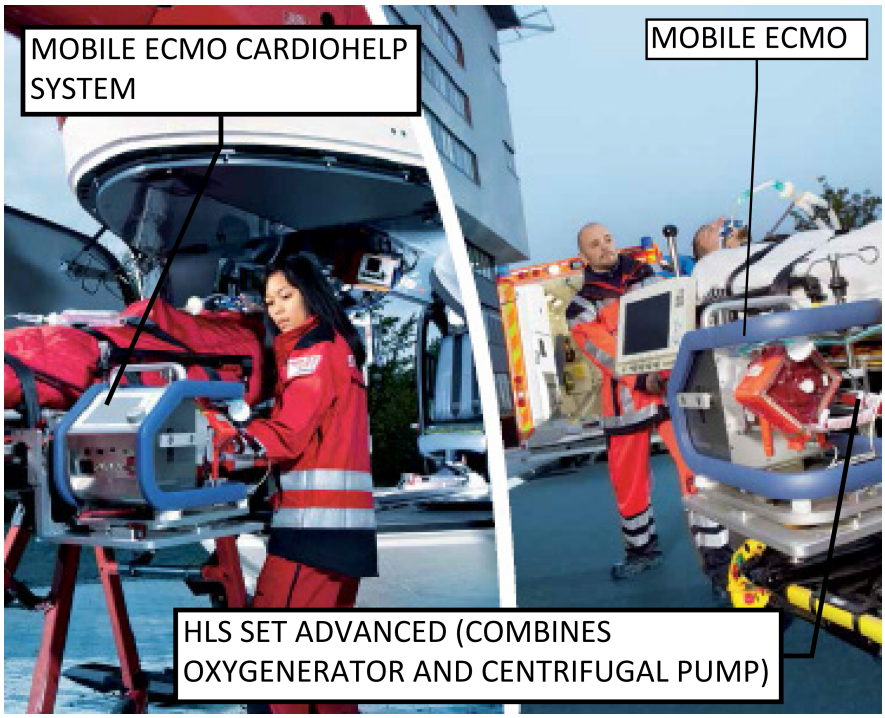


Figure 6: The portable extracorporeal membrane oxygenation support machine. Reprinted with permission from Maquet Czech Republic s.r.o.

electro-anatomical mapping, and catheter ablation of nontolerated ventricular tachycardia [97]. VA-ECMO has also been successfully used in sepsis-associated cardiomyopathy [43, 92], pulmonary hypertension [4] and pulmonary embolism [77, 64].

2.2 Hemodynamic and cardiac performance parameters in ECMO treated individuals with cardiac arrest and cardiogenic shock

VA-ECMO is a powerful life support system, which is increasingly used in the therapy of critical conditions caused by advanced cardiac pump failure such as severe and rapidly progressing CS or CA refractory to standard resuscitation techniques [78, 20]. Basic indications for VA-ECMO are 1) CS, 2) CA [41, 85] 3) myocarditis, 4) patients who cannot be weaned from cardiopulmonary bypass after cardiac surgery [85].

Cardiogenic shock.

CS is a clinical state which occurs as a result of tissue hypoxia; it is caused by primary cardiac pathology which leads to inadequate cardiac output (CO) and systemic perfusion in the presence of adequate intravascular volume [41, 55].

During CS the heart suffers from the ineffectiveness of the cardiac pump function; the other organs such as the gut, liver, kidneys, and brain are at risk due to insufficient perfusion (multiorgan dysfunction syndrome). Furthermore, the risk of pneumonia associated with the occurrence of CS is increased. As a result of reduced coronary perfusion, CO is further reduced, and multiorgan dysfunction or/and multiorgan abnormalities are complicated by metabolic acidosis and acute coagulopathy. All these conditions exacerbate each other in a deadly vicious circle [78].

CS is primarily defined based on hemodynamic parameters. In addition to classical CS markers - pressure and heart rate (HR), there are additional markers of multiorgan dysfunction and circulatory disturbance - central venous oxygenation, urine output, liver enzymes, and serum lactate [78].

There is some variability in the definition of CS in clinical trials [41, 55].

I. Low blood pressure (<90 mmHg) for at least 1 hour refractory to fluid administration; low blood pressure (<90 mmHg) caused by cardiac dysfunction; low blood pressure (<90 mmHg) associated with hypoperfusion or a cardiac index (CI) less than 2.2 L/min/m^2 and pulmonary artery wedge pressure (PAWP) higher than 18 mmHg [41].
II. A decrease of cerebral and tissue oxygenation down to 50 %, increased serum lactate level, mixed venous oxygen saturation (SvO_2) less than 55 %, encephalopathy symptoms, CI lower than 2.2 liter/min^{-1}/m^{-2} despite adequate preload, and systemic signs of low CO [85].
III. A pathological state with the most common cut-off points for systolic blood pressure (SBP) less than 80-90 mmHg for ≥30 min and a significantly decreased CI (<1.8 liters/minute/m^2 without support or <2.0 liters/minute/m^2 with support), elevated serum lactate (≥2 mmol/liter) [41, 55].

In patients with CS, as a result of hypoperfusion of the myocardium and peripheral organs, the process of anaerobic metabolism in the tissues of organs begins, which may lead to lactic acidosis. The accumulation of lactic acid can lead to swelling of mitochondria and degeneration, causing glycogen depletion, which in turn may worsen the function of the myocardium and suppress glycolysis, which leads to an irreversible ischemic lesion. Serum lactate level is an important predictor of CS. A lactate level > 6.5 mmol/L in CS patients is a very strong independent prognostic factor of mortality [41].

Clinical signs indicative of CS include signs of systemic hypoperfusion, such as cold skin, and/or oliguria, elevated jugular venous pressure, altered mental state. Rales, indicating pulmonary edema, may or may not be present. Neither auscultation nor chest radiograph detects pulmonary edema in 30 % of patients with CS. CS can occur as a result of a wide variety of cardiac disorders, including acute coronary syndrome, valvular disease, myocardial and/or pericardial disease, congenital lesions, or mechanical injuries of the heart [41, 55].

In patients with severe CS, ECMO is routinely employed [78]. ECMO in CS is used to achieve the following goals:

- To stabilize hemodynamics and to improve the tissue perfusion of end organs functions.

- To limit LV wall stress; consequently, reducing myocardial oxygen demand.
- To improve coronary perfusion.
- To gain time for:
  - Complete revascularization.
  - Comprehensive assessment (Neoro, Surgical, or Adv HF) [20].
- As a bridge to:
  - Recovery.
  - Decision (percutaneous coronary intervention, elimination of ventricular tachycardia, percutaneous or surgical elimination of critical valve defect, and other heart surgery).
  - Intervention.
  - Left ventricular assist device implantation.
  - Heart transplantation [85].

Cardiac arrest.

CA is a major cause of unexpected death in developed countries with a low probability of patient survival [31]. CA refractory to standard resuscitation techniques is an emerging indication for mechanical circulatory support [78]. The survival of patients, who have suffered in-hospital or out-of-hospital CA, depends on several factors, such as the time of recognition of the CA, time of initiation of cardiopulmonary resuscitation, time of the first fibrillation and rhythm presentation [31]. Out-of-hospital CA occurs with an estimated incidence of 500,000 per year in Europe, with two-thirds having a primary cardiac cause. Despite interventional therapy and modern intensive care, mortality after out-of-hospital CA remains high [78].

The urgent initiation of cardiopulmonary resuscitation right after an collapse and the availability of automated external defibrillators is an essential factor in increasing the probability of survival of the person who has suffered CA. The first electric shock should be applied as soon as possible in order to minimize the time of hypoperfusion and hasten the return of spontaneous circulation in selected patients; therefore to prevent failure of the LV and the

development of CS. The CA results in myocardial and end organs ischemia, which leads to acidosis, an adverse metabolic, and vasoplegia. Cardiac hypoperfusion results in an inability of the heart to respond to the needs of circulation, which is enhanced peripheral ischemia. After the return of spontaneous circulation, the restoration of system perfusion is significant in order to reduce multiorgan dysfunction. Complete cardiac revascularization is strongly recommended in selected patients after CA, but it is important to care for other end organs such as the kidneys, the liver, the intestines, and the brain [78]. CA refractory to standard resuscitation techniques is an indicator of the purpose of ECMO; it's prescription is useful when the laboratory tests indicate lactate less than 21 mmol/L, pH more than 6.7, SvO_2 more than 8 % [85].

2.3 Left ventricular overload during VA-ECMO therapy

Notwithstanding the fact that ECMO has many advantages, such as the fast set-up of the system and efficient hemodynamic support [78]; it also has a significant risk of complications. An important pitfall of the ECMO, which can highly impair patient outcome, is inappropriate LV unloading. VA-ECMO can cause LV overload, primarily due to the increased afterload (Figure 7) [78, 44, 13, 9].

It should be recognized that the overload of LV during VA-ECMO is estimated in about 70 % of cases and can significantly affect the survival of patients [24]. In the presence of severe LV dysfunction, the LV is unable to eject a sufficient volume of blood against the increased afterload caused by the ECMO [41, 68, 44, 13, 34, 9, 50, 112, 87, 99]. The measure of the reduction in LV stroke volume (SV) is dependent on the degree of the contractile function violation, the presence of mitral/aortic regurgitation, and the magnitude of extracorporeal blood flow (EBF) [61, 87].

Simulation [86], animal [87], and human [6] studies show unsatisfactory LV unloading during high-flow VA-ECMO, which impairs several parameters of LV performance. In patients with extremely low systolic LV function the aortic valve can remain closed even during

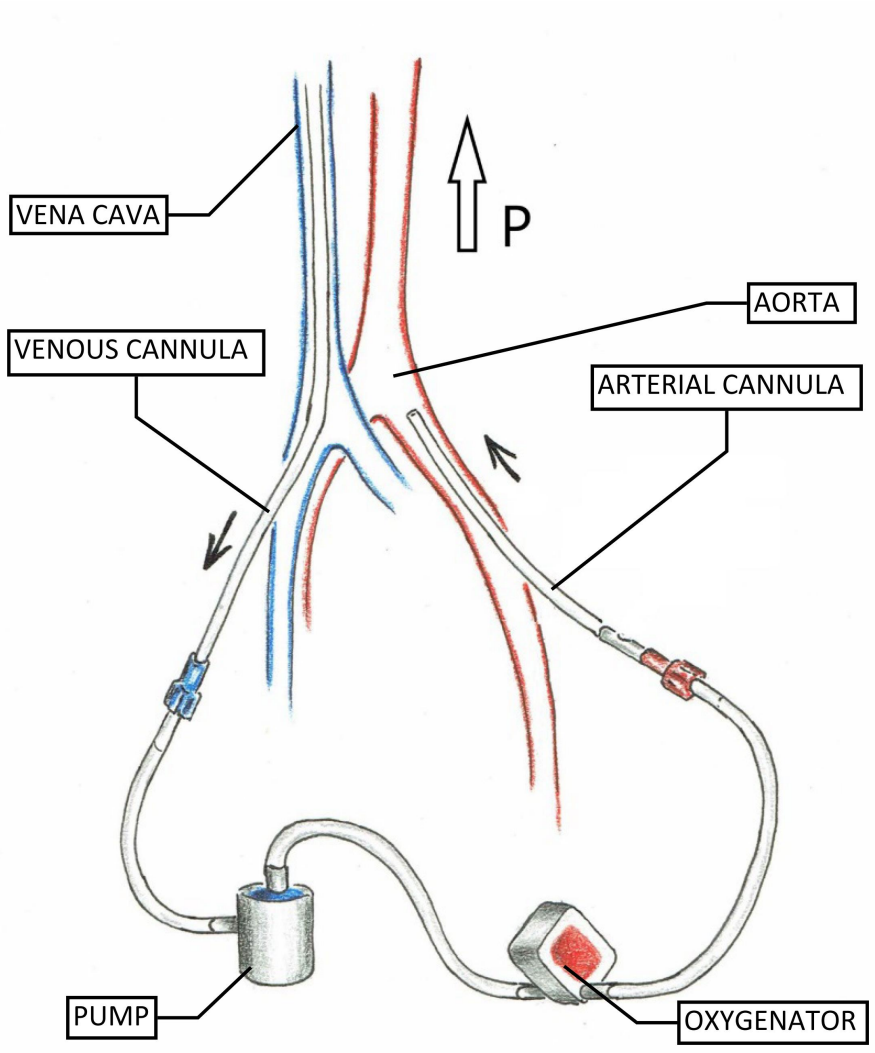


Figure 7: Left ventricular overload in consequence of the VA-ECMO application

systole [111, 78, 73]. The extreme LV overload significantly deteriorates the ventricular contractile function, which causes stagnation of blood in the LV, making the left heart chamber a favorable environment for the formation of thrombus. This event has been demonstrated during experiments with animal models and has been confirmed in human studies [73]. The inappropriate LV unloading potentially results in increased LV filling pressures, severe LV distension, increased wall stress, severe pulmonary congestion, and pulmonary edema, increased myocardial oxygen consumption [68, 107, 52, 87, 6, 32], despite a reduction of preload [73, 78, 44, 13, 9] and the presence of sufficient systemic circulation [78]. If the CS has occurred as a result of decompensation in chronic heart failure, the LV is likely to be compliant and the

mitral valve is frequently incompetent as a result of chronic annular dilation and mitral valve leaflet tethering. The resultant mitral reflux would decompress the LV to some extent but may result in elevation of left atrial pressure and pulmonary edema [68, 13, 61, 107, 32, 21, 103]. In contrast, in acute CS, such as following acute myocarditis or myocardial infarction, the LV is likely to be noncompliant and the mitral valve likely to be competent. LV distension in this setting will result in a significant rise in intraventricular pressure and wall tension, which could be detrimental to damaged myocardium. In addition, the rise in LV pressure could reduce coronary blood flow, causing myocardial ischemia, particularly in the subendocardial area [50, 107, 120]. The development of LV overload and distension could also be potentiated by the presence of aortic regurgitation [104]. Increased LV afterload, together with severe systolic dysfunction, may result in LV overload and can lead to refractory pulmonary edema, fatal pulmonary hemorrhage, and LV clotting [21, 111, 61]. LV overload during VA-ECMO therapy represents a critical condition that frequently requires urgent intervention to unload the LV; LV unloading is a crucial issue during VA-ECMO.

2.4 The methods of left ventricular unloading during VA-ECMO therapy

ECMO can increase LV afterload and may result in LV loading. These negative sequelae of VA-ECMO can be prevented and resolved by LV venting or active LV unloading [78, 8]. It has been shown that early decompression is associated with reduced time on ECMO and the reduction of ECMO-associated complications [38]. To date, several approaches have been proposed to unload an overloaded LV during VA-ECMO therapy.

Atrial septostomy.

LV decompression can be achieved by creating left atrial and right atrial communication - a septal defect or patent foramen ovale; whereas, it is widely known that, left-sided filling pressure is higher than right-sided filling pressures in the heart. The favorable effect of such a left-to-right shunt on LV decompression has been reported in children and adults [24]. Atrial

shunt can be created artificially with percutaneous blade or balloon septostomy [52, 103]. Seib et al. [103] reported series of 10 patients with severe LV dysfunction (seven myocarditis, three dilated cardiomyopathy) who required circulatory support with ECMO and who underwent left heart decompression with blade and balloon atrial septostomy (BBAS). BBAS was performed prior to initiating ECMO in three patients and during ECMO in seven patients. A femoral venous approach was used in all patients. Transseptal puncture was required in nine patients while one patient had a patent foramen ovale. The procedure was successful in all patients and led to LV decompression and pulmonary decongestion. Left atrial mean pressure fell from a mean of 30.5 mmHg to 16 mmHg. Left atrial to right atrial pressure gradient fell from a mean of 20 mmHg pre-BBAS to 3 mmHg post-BBAS. Artificial atrial septal defect size ranged from 2.5 mm to 8 mm [103]. It should be realized that atrial septostomy has been reported as one of the first LV unloading techniques during VA-ECMO but remains technically demanding, limited efficacy, and experience is largely confined to specialized centers and pediatric patients [24].

Left atrial venting.

Unloading can be achieved by placement of an additional draining cannula through the atrial septum. With guidance by bedside transoesophageal echocardiography, a percutaneous atrial transseptal cannula can be placed and connected to the venous site of the ECMO circuit [24, 112, 7]. Swartz et al. [112] reported a case involving a 13-year-old girl who presented with CS. VA-ECMO was initiated, but after six days, severe LV distension resulted in decreased VA-ECMO flows. With guidance by bedside transesophageal echocardiography, a percutaneous atrial transseptal cannula was placed and connected to the venous site of the ECMO circuit, thus decompressing the LV. The patient improved, was weaned from VA-ECMO five days later and was discharged from the hospital [112]. Aiyagari et al. [7] described a series of seven patients with cardiac failure on VA-ECMO with left atrial hypertension. All patients underwent left atrial decompression with transseptal puncture and placement of a

drain (from 8 Fr[1] to 15 Fr). The average time from ECMO cannulation to left atrial decompression was 11 hours. The average initial left atrial pressure was 31 mmHg. Successful drain placement was achieved in all patients with no major periprocedural complications. Echocardiographic improvement in left atrial dilation was achieved in five (71 %) patients. Inability to decompress the left atrium was fatal in two patients. Four (57 %) patients were decannulated and three (43 %) survived to hospital discharge [7].

LV venting.

The LV can be vented directly by placing a transaortic vent through the axillary artery or by echocardiography-guided insertion of a pigtail catheter into the LV through the aortic valve and connected to the venous site of the ECMO circuit [78, 35, 13]. Fumagalli et al. [35] reported a case in which extracorporeal life support was used as a bridge to heart transplantation, for a patient with CS. LV decompression, during ECMO, was achieved with a catheter placed percutaneously through the aortic valve into the LV. The blood from the LV was drained following the normalization of left heart filling pressures. The catheter application led to the resolution of the patient's pulmonary edema. Subsequently, the patient underwent successful heart transplantation, and then the patient underwent mechanical circulatory support for a further seven days [35]. Barbone et al. [13] proposed LV unloading with a 7 Fr pigtail catheter inserted into the LV via the femoral artery contralateral to the arterial outflow cannula. This approach was used in three patients with CS due to acute myocardial infarction. As a result of pigtail catheter application, the resolution of LV distension and prevention of lung congestion without major complications were achieved in all three cases.

Pulmonary artery drainage.

One of the approaches for LV decompression is the percutaneous insertion of the second venous cannula into the pulmonary artery and connection of this cannula to the venous site of the ECMO circuit [11, 32]. Avali et al. [11] reported a case involving a 43-year-old woman

[1]The French scale (Fr) is a system which is commonly used to measure the diameter of a cannula or catheter; 1 Fr=1/3 mm

treated with ECMO for refractory CS after left pneumonia and severe sepsis. A 15 Fr venous cannula was placed percutaneously to the pulmonary artery and connected to the ECMO circuit to decompress the left heart, and to facilitate LV function. After myocardial recovery, the patient was weaned and ECMO was removed on day sixteen [11]. Fouilloux et al. [32] described unloading of the LV with a cannula inserted into the pulmonary trunk through the inferior vena cava with a femoral approach in a two-year-old girl with restrictive cardiomyopathy. A few hours later, the chest X-ray improved and five days later, recovery of the LV function allowed removal of the pulmonary artery cannula [32].

Intra-aortic balloon pump.

Intra-aortic balloon pump (IABP) counterpulsation is a device that inflates and deflates a 30 cm to 50 cm balloon in the descending aorta. The balloon inflations and deflations are synchronized with the cardiac cycle and, therefore, deflation just before systolic ejection may decrease afterload and improve LV ejection. Moreover, increased diastolic pressure on IABP could also improve coronary blood flow. Despite the controversial data from the Intraaortic Balloon Pump in cardiogenic SHOCK (IABP-SHOCK) II trial [114], IABP currently remains one of the most commonly used mechanical circulatory support devices in the treatment of acute heart failure. When administered in a timely manner, it can play a critical role in the rescue of patients with acute myocardial damage. It has been shown in animal models that insertion of IABP during VA-ECMO support may improve several parameters of LV performance [99]. Currently, several centers use IABP to reduce LV afterload during VA-ECMO therapy. In a group of 219 patients treated with VA-ECMO after cardiac surgery, Doll et al. [23] found that the use of IABP during ECMO support was associated with a significantly higher survival rate. Ma et al. [62] reported 54 adult patients with acute heart failure who received combined ECMO and IABP support, all of whom showed improvements in terms of overall circulation. Thirty-four of the patients were successfully weaned from mechanical circulatory support, and 21 (39 %) survived to hospital discharge [62]. The study by Petroni et al. [92] showed that adding an IABP to peripheral VA-ECMO was as-

sociated with improved LV function. Discontinuation of intra-aortic balloon pumping was associated with higher PAWP (19±10 mmHg versus 15±8 mmHg; P=0.01), increased LV end-systolic (51±13 mmHg versus 50±14 mmHg; P=0.05) and end-diastolic (55±13 mmHg versus 52±14 mmHg; P=0.003) diameters, and decreased pulse pressure (15±13 mmHg versus 29±22 mmHg; P=0.02) [92]. In contrast, Park et al. [91] did not find any mortality or morbidity benefit with IABP in the group of 96 VA-ECMO-treated patients with CS due to acute myocardial infarction. Recent clinical data provide conflicting evidence and partly contradict this picture of post-cardiotomy failure and infarct-related shock. There are extensive analyses that do not unequivocally support the routine combination of VA-ECMO and IABP as a clinical standard, whereas another recent analysis favors its application and suggests a survival benefit. The IABP may also have a negative impact on the spinal cord and cerebral blood flow during VA-ECMO, especially when the native cardiac function is severely impaired [24].

Percutaneous LV support devices.

Percutaneously inserted pumps have been developed to drain the LV and eject blood from LV into the ascending aorta [78]. Impella LP 2.5 (Abiomed Inc, USA) is a catheter-based transaortic microaxial flow pump that can be introduced through a percutaneous femoral approach. The device is placed across the aortic valve and pumps up to 2.5 L/min of blood from the LV into the ascending aorta. The Impella 2.5 has been reported as an adjunct to peripheral VA-ECMO in order to unload the LV representing the second largest clinical experience as LV unloading intervention during VA-ECMO following the IABP [24]. Koeckert et al. [50] reported the use of Impella LP 2.5 for LV decompression in a 70-year-old man with decompensated heart failure who was placed on VA-ECMO for a CS with severe pulmonary edema and respiratory failure. Both devices were successfully weaned on day 5 after myocardial recovery [50]. Narain et al. [81] described a case involving a 31-year-old man with fulminant myocarditis treated with the Impella device and VA-ECMO. On full mechanical circulatory support, the hemodynamic status improved and both systems were explanted

after 48 hours [81]. Modern Impella CP is abble to increase CO by up to 3.5 L/min [71]; the Impella 5.0 provides up to 5 L/min [36]. The increasing survival rate was reported the in patients with CA and CS with the Impella CP [117] and with the Impella 5.0 [36]. The Impella device should, therefore, be considered as a powerful LV unloading device during VA-ECMO [24]. Nonetheless, several studies reported that the application of Impella can leads to significant hemolysis [12, 83] .

Various methods for left heart decompression are known, but there is no consensus about the appropriate method and timing of decompression [21]. Until the present time, all of the methods currently in use requires further intervention; this increases the invasiveness and thus can lead to additional complications.

Therefore, the development of an alternative less-invasive method of left heart unloading is a significant issue in VA-ECMO therapy.

2.5 Peripheral cannulas in extracorporeal life support

As outlined earlier, each of the currently reported methods for LV unloading during ECMO require further intervention, which increases the invasiveness of the ECMO therapy and thus can lead to additional complications such as an infection, bleeding and prolonged recovery times. An alternative and novel less-traumatic method to prevent LV overload during ECMO is to modify the configuration of the arterial reinfusion peripheral cannula.

ECMO cannulas are used to provide the interface between the patient and the extracorporeal circuit. Cannulas in ECLS devices are used in many forms for direct cannulation, peripheral cannulation, venous cannula, an arterial cannula, for adults and children. They are used in open surgery, laparoscopic surgery, and in different interventions. The emergency use of ECMO usually requires percutaneous cannulation of the femoral vessels [72]. The main advantage of peripheral cannulation is that it does not require open chest surgery for initiation of ECMO [49, 44]. The peripheral ECMO cannulas provide greater versatility for cannulation techniques and facilitate working towards striving for smaller incisions.

2.5.1 Types of peripheral cannulas

There are several types of modern peripheral cannulas that are used in practice.

Single-lumen peripheral cannulas.

Single-lumen peripheral cannulas are used to provide venous and arterial access for VA-ECMO or multiple site venous access for VV-ECMO [100, 74, 58, 56]. The deoxygenated blood is drained through an inflow cannula. The oxygenated blood is returned via an outflow cannula [17] (Figure 8).

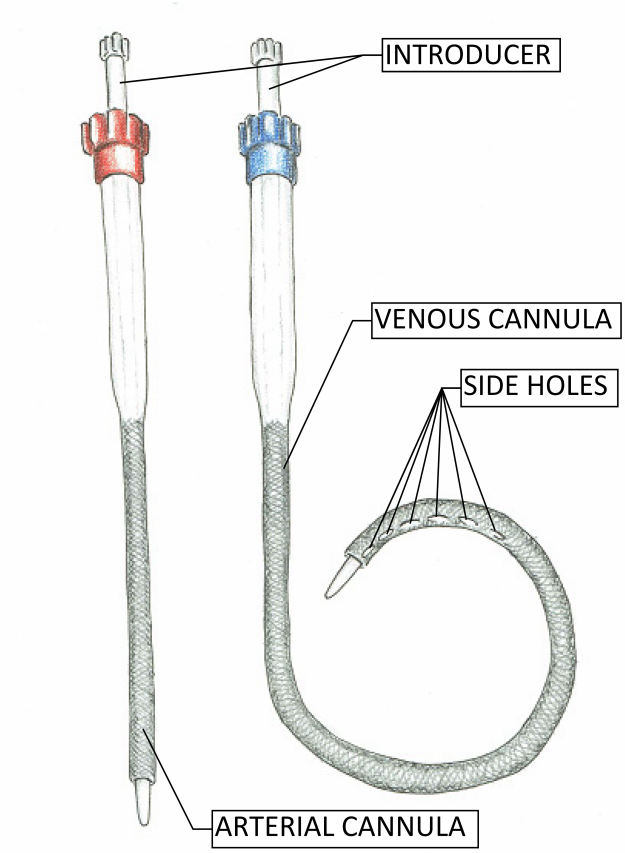


Figure 8: Percutaneous arterial cannula (on the left) and percutaneous venous cannula (on the right)

Basically, a single-lumen peripheral cannula is an elastic tube with an orifice at the tip [58, 3] and side holes; it has been shown that the side holes decrease the mechanical stress on blood components [51].

The alternative type of single-lumen peripheral cannula is a Smartcanula (Smartcanula®, Smartcanula LLC, Lausanne, Switzerland) (Figure 9). It has a wire structure and is a virtually wall-less device, in contrast with the current design of percutaneous cannulas. It is a virtually wall-less cannula with an open wall (mesh structure) which allows collapsed insertion and expansion in situ [3, 15]. The design of Smartcanula allows a decrease in the pressure drop throughout the cannula; thereby, increasing the EBF.

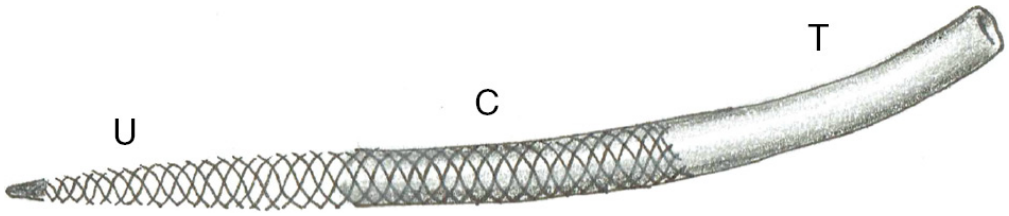


Figure 9: Smartcanula. T - tubing, C - covered, U – uncovered

Double-lumen peripheral cannulas.

Double-lumen cannulas combine both drainage and reinfusion lumens into one cannula [51] (Figure 10). This type of cannula is less-invasive and provides veno-venous support via a single jugular venous access site [58]. The right jugular vein cannulation has a much shorter route to the right atrium than femoral cannulation. It can accommodate a much larger cannula for higher performance [22]. Using this type of cannula reduces the circuit size, which minimizes blood cells and circuit interaction. Nevertheless, the cannula size is much larger than that of the standard peripheral cannula and it is not very elastic which complicates the double-lumen cannulas admission [22, 49]. If the fluoroscopy is not available, the insertion of the double-lumen cannula is not recommended, because of the risk of right ventricular perforation [49].

2.5.2 Cannula position

In the veno-arterial configuration of ECMO, an inflow peripheral cannula is inserted via the femoral vein or via the right internal jugular vein with its tip in the right atrium. The outflow cannula is inserted via the femoral artery with the tip position in the iliac artery or in the

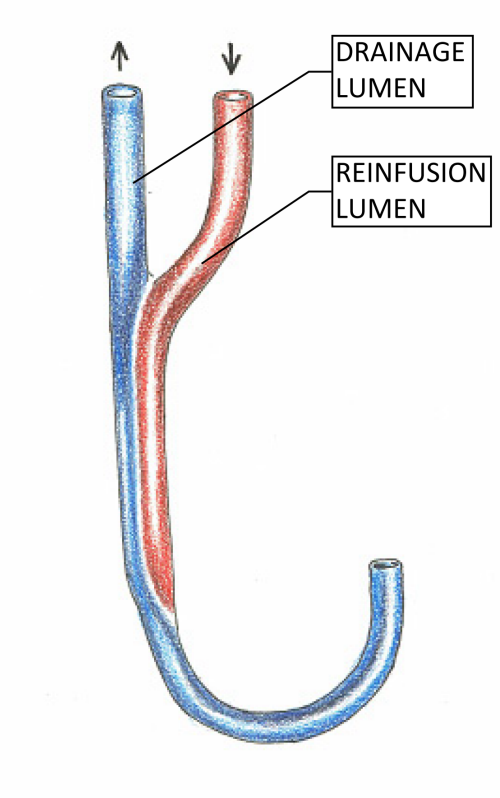


Figure 10: Double-lumen cannula

distal abdominal aorta. Another approach of an inflow peripheral cannula insertion is via the subclavian artery with the tip position into the ascending aorta [41, 44, 25, 21, 72, 63, 14].

In the veno-venous configuration of ECMO, the peripheral cannulas are usually introduced via the femoral and jugular veins with the cannula tips at the border between the right atrium and the superior and inferior caval veins to minimize recirculation [80]. In the case of using a double-lumen cannula, the right-sided jugular vein is commonly used for insertion [44, 60, 63, 79].

2.5.3 Material

Modern cannulas are of a strong, one-piece polyurethane molding construction. The cannulas are manufactured from biocompatible silicone polyurethane polymer, which may be coated with polymers that may reduce platelet activation and the inflammatory response at the blood-cannula interface. Cannulas combine flexibility and resistance, e.g. polyurethane has

high material strength at room temperature and becomes more malleable at body temperature (this aids the insertion of the cannula) [51, 58, 14].

The cannulas are constructed with reinforced stainless steel (SS) wire. Wire reinforcement of the cannula walls is used to prevent kinking or collapse [51, 58, 1]. This type of design provides a longer-term ambulatory application [22]. The cannulas that were manufactured from non-wire-reinforced polyurethane became deformed following insertion. Kinking and collapse of the cannula can lead to catastrophic interruption of the flow of ECMO [58].

A rigid cannula introducer is made of polyvinylchloride with an embedded SS rod [22].

2.5.4 Surface coating

Although modern cannulas are made of biocompatible materials, surface coatings are applied on the cannula to reduce the activation of the clotting; control of blood clotting is essential during extracorporeal life support [51, 14].

Currently, the trend is to prevent blood clotting without using anticoagulants [2]. Heparin-coated surfaces result in reduced complement and inflammatory activation due to its anti-inflammatory properties. Nevertheless, heparin causes the development of osteopenia and thrombocytopenia [51, 123]. Heparin-coated surfaces can trigger release of cytokines, which exert a damaging effect on the lungs [98]. Furthermore, heparin-based coatings can leach into the blood and result in the exposure of the blood to extremely high heparin doses (> 50 U/kg) [59]. This can cause excessive bleeding and can be lethal.

Nowadays biocompatible surfaces more closely resemble the physiological endothelium. The coatings have a hydrophilic outer layer and some contain negatively charged groups to repel negatively charged proteins and platelets and thereby create a layer between the components of human blood and the artificial surface. For example, “Balance Biosurface” by Medtronic and “X Coating” by Terumo [51].

An alternative coating material for ECLS cannulas is bivalirudin (BVLD). BVLD is a short, synthetic peptide, derived from hirudin, that is potent, highly specific and a reversible

thrombin inhibitor which is used as a surface coating. It was reported that BVLD was covalently conjugated on plasma polymerized allylamine (PPAam) coated 316L SS to develop an anticoagulant surface. The BVLD-PPAam-modified 316L SS disk was implanted in the femoral artery of dogs for 5 weeks. The anticoagulant surface prevented thrombosis formation by rapidly growing a homogeneous and intact endothelium on its surface [51, 123].

The next nonheparin coating is tethered-liquid perfluorocarbon (TLP). The TLP resisted adhesion of fibrin and platelets, suppressed biofouling and reduced thrombosis and bacterial adhesion. Medical materials with a TLP coating have antithrombogenic and anti-biofouling surfaces that do not require co-administration of antiplatelet, anticoagulant or antibiotic medications. It was reported that the TLP-coated tubing and catheters in large blood vessels in pigs retained their ability to prevent occlusive thrombus formation for 8 hours without using blood thinners such as heparin [2, 59].

2.5.5 Dimensions

The size and location of the inflow and outflow cannulas impact tissue oxygenation as well as the degree of cardiac support provided. The intent of appropriate cannula choice is to provide full flow without damaging the cells, particularly erythrocytes, from excessive shear stress and turbulence [44]. The currently used peripheral ECLS cannulas for adults typically range from 18 Fr to 29 Fr for venous and 13–23 Fr for arterial cannulas [44, 14, 65]. The double-lumen cannula sizes for adults are from 13 Fr to 31 Fr for Avalon Elite Bi-Caval Dual Lumen Catheters [66] and from 13 Fr to 32 Fr for OriGen dual lumen catheters [84].

For adult patients, the cannula length is variable and may range from 50 cm for inflow and from 18 cm for outflow cannulas depending upon the manufacturer, the anatomy of the patient and the vasculature [14]. The insertion length of peripheral cannulas for adults may vary in range from 38 cm to 55 cm for inflow and from 15 cm to 23 cm for outflow cannulas [65]. For double-lumen cannulas, Avalon Elite Bi-Caval Dual Lumen Catheters, the insertable length range is from 11 cm to 31 cm [66]. The insertable length of OriGen dual

lumen catheters is from 8 cm to 25 cm [84].

By minimizing the cannula thickness, the internal diameter increases, thereby obtaining the highest flow efficiency and cannula flexibility with the smallest anatomical footprint [22, 45]. Nowadays, the ultrathin wall of percutaneous cannula achieves a thickness of 0.48 mm for adult cannulas and 0.38 mm for pediatric cannulas [75]. Double-lumen cannula for VV-ECMO has a wall thickness of 0.7 mm with a thin membrane sleeve of the infusion lumen inside the main body with a wall thickness of 0.3 mm [22].

There are a lot of opinions regarding recommendations for cannula size. The increasing in cannula size decreases the resistance of the cannula; nevertheless, it increases the risk of vessel damage. The size of the cannula is recommended depending on the patient's anatomic features and the weight or body surface area [14, 17, 37]. Depending on the patient's anatomical parameters, the cannula should reach from the peripheral insertion point to a central location. Some data suggest that the cannula size should be determined in relation to the actual size of the vessel [14, 37, 58, 51]. Nevertheless, because many different cannulas exist, studying the flow chart of each cannula is commonly used to determine the appropriate size [76]. The cannula provides a resistance within the ECMO circuit and, therefore, creates a pressure drop (the difference between the pressure entering the cannula and that of leaving) across it [60]. The pressure-flow characteristics of cannulas are dependent on their length and internal diameter [113]. The widest and shortest possible cannula is the best choice to achieve the maximum flow.

Pressure drop versus flow charts of the outflow and inflow cannulas from the manufacturers is based on evaluations using water as the testing solution [95] at ambient temperature. The blood flow in the circuit during ECMO may vary depending on blood viscosity, the patient's anatomy, and circuit configuration. Blood flow regulated over time to meet physiological goals such as the stabilization of systemic perfusion and improving end organ functions. With a higher pressure across the cannula, there is an increase in jetting at the tip, that can cause intimal damage to the vessel [60]. The high-pressure flow becomes turbulent [51] and

may damage the red blood cells. In addition, it can be the cause of microbubbles [85] and induce bubble emboli. The accepted limit of venous cannula pressure drop is 100 mmHg. This should not ordinarily be exceeded [60]. Newetheles, in the arterial cannula, greater pressure drop values are allowed. In conclusion, the largest possible cannula can be recommended to maximize blood flow. Nonetheless, small cannulas provide support by reducing bleeding complications [113], the risk of vascular damage, ischemia, and obstruction of arteries [85].

2.6 Conclusions

CS and CA share many pathophysiological features, and in this context, VA-ECMO is a powerful circulatory support system. ECMO is an effective tool for systemic circulation support and provides gas exchange. However, especially in patients with most severe heart dysfunction, initiation of VA-ECMO may be associated with LV overload with all of its consequences including severe pulmonary edema and respiratory failure. VA-ECMO might increases LV afterload and may result in LV distension, and pulmonary edema, which can be prevented and resolved by LV venting or active LV unloading.

To date, various techniques have been proposed to decrease LV distension and improve its function during ECMO therapy. However, each of these methods increases the invasiveness of the procedure; the additional interventions, which are required by currently used methods for LV unloading during ECMO, increase the risk of complications such as infection, bleeding and longer recovery times.

An alternative method to prevent LV overload during ECMO is to modify the configuration of the arterial reinfusion peripheral cannula. Today's peripheral cannula has a one-piece, biocompatible, thin-walled, kink resistant, wire-wound body. The construction of modern cannulas maximizes flow rates and flexibility.

3 Aims and objectives

This doctoral thesis aims to develop an alternative method of LV unloading or LV overload reduction, which has the potential for reducing the invasiveness of LV unloading during VA-ECMO therapy. It is intended that the findings will contribute to the mitigation of ECMO complications such as LV overload; furthermore, it is intended to help eliminate the complications, of the current methods for LV decompression, such as an additional source of bleeding, infection, and the longer recovery times of ECMO treated patients.

This aim leads to the following core doctoral thesis objectives:

1. To describe hemodynamic and cardiac performance parameters in ECMO treated individuals with CA and CS.
2. To describe currently existing methods for LV unloading in VA-ECMO treated individuals.
3. To investigate the impact of ECMO therapy on LV performance in large animal models of CS.
4. To propose an alternative method of LV unloading or LV overload reduction, which has the potential for reducing the invasiveness of LV unloading during VA-ECMO therapy.
5. To create a model, based on data from large animal models of CS, and establish the value of LV decompression by using the proposed alternative method of LV unloading.
6. Based on the modeling and simulation, to identify circumstances under which to increase the value of LV decompression by using the proposed alternative method of LV unloading.
7. To investigate the impact of the proposed alternative method of LV unloading during VA-ECMO on LV performance in large animal models of CS.

The long-term goal of the research is to manufacture the proposed invention and involve it in medical practice.

4 Material and methods

In this chapter material and methods for modeling, simulation, and experimental study with models of CS, described in the doctoral thesis, are presented. Swine (Sus scrofa domestica) with an average weight of forty-five kilograms were used as the experimental animals. The drafts of DLAC for ECMO were created in AutoCAD software. Modeling and simulations have been implemented using the Modelica modeling language (Modelica Association) in the Dymola (Dassault Systemes) modeling environment and using the components from Physiolibrary 2.3.1. The data were analyzed by using GraphPad Prism 5.0 software (GraphPad, USA) and R 3.5.3 software (The R Foundation, Vienna, Austria).

4.1 Experimental study with large animal models

The experimental study was approved by the Charles University 1st Medical School Institutional Animal Care and Use Committee and was performed at the Animal Laboratory, Department of Physiology, 1st Medical School, Charles University in Prague and Na Homolce Hospital, Prague, Czech Republic, in accordance with Act No 246/1992 Coll. on the protection of animals against cruelty. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1985). Animals were subjected to VA-ECMO implantation under general anesthesia and artificial ventilation (Figure 11). Subsequently, LV dysfunction was induced to result in acute severe CS followed by signs of tissue hypoxia. Hemodynamic and cardiac performance parameters were then measured and processed.

4.1.1 Animal model

The structure and function of the swine, such as size, coronary artery distribution, feeding patterns, tidal volumes digestive physiology, respiratory rates, dietary habits, propensity to obesity, kidney structure and function, pulmonary vascular bed structure are similar to hu-

Figure 11: Animal Laboratory, Department of Physiology, 1st Medical School, Charles University in Prague and Na Homolce Hospital with a large animal model of cardiogenic shock

man structure and function. These facts make pigs good models for the research. Pigs have been successfully used as models for the evaluation of alcoholism, septic shock, diabetes, dermal healing, absorption process, digestion process, osteochondrosis, total parenteral nutrition process, reflux nephropathy, organ transplantation, obstructive nephropathy, atherosclerosis, exercise, gingivitis, hypertension, melanoma, and hemorrhagic hypotension [102].

The porcine cardiovascular system is similar to the human cardiovascular system in size, structure, and functionality; this provides a comparable model in cardiovascular studies such as the investigation of cardiovascular physiology and pathophysiology, human coronary artery pathology, recording and analysis of responses to tests of cardiac function, the ventricular function and hemodynamic vascular parameters indication [101], the development of an improved diagnostic and surgical procedure [102], the modernization of clinical methods and techniques [101].

Blood gases, pH, circulating blood volume (67.3±3.7 ml/kg in a swine, 69.1±6.6 ml/kg in a human) and plasma volume (49.6±3.1 ml/kg in a swine, 41.1±4.3 ml/kg in a human) are similar in a swine and that of man; although swine hematocrit (27±3 % in a swine, 46±5 % in a human) and hemoglobin (8.5±0.8 g/dl in a swine, 15±2 g/dl in a human) are

slightly lower. The CO of swine is higher than in humans (147±22 ml/min/kg in a swine, 93±20 ml/min/kg in a human), which is associated with an increase in HR (105±10 b/min in a swine, 70±14 b/min in a human) and SV. Systemic pressure (systolic pressure 127±8 mmHg in a swine, 126±14 mmHg in a human, diastolic pressure 86±7 mmHg in a swine, 79±10 mmHg in a human) and pulmonary pressure (mean pulmonary artery pressure 16±4 mmHg in a swine, 16±2 mmHg in a human) of swine is well in line with human pressure; the development of pressure is the main factor determining the cardiac work, so the relationship between swine and human cardiac metabolism and coronary blood flow is also quite similar [101].

Female swine (Sus scrofa domestica) were used in the experiments. The age of animals was four to five month; the average body weight was forty-five kilograms. For induction of general anesthesia, intramuscular administration of midazolam (0.3 mg/kg) in combination with ketamine hydrochloride (15–20 mg/kg) were used. Intravenous boluses of propofol (2 mg/kg) and morphine (0.1–0.2 mg/kg) were administered to initiate the anesthesia; followed by orotracheal intubation of the animals. The maintenance of anesthesia was achieved by a continuous intravenous infusion of propofol (8–10 mg/kg/h) and morphine (0.1–0.2 mg/kg/h); the doses were titrated, taking into account physiological parameters, photoreaction, corneal and palpebral reflexes, lacrimation and spontaneous movement. The animals were euthanized after the experimental studies by the injection of potassium chloride (2 mEq/kg), in combination with general anesthesia [87, 88, 93].

Multiple sheath insertions were performed using bilateral femoral (arterial and venous) and jugular approaches; the Seldinger insertion method was used to obtain access to vessels. An unfractionated heparin bolus (100 U/kg) was administered intravenously to prevent thrombosis, especially at the site of sheath insertion. The activated clotting time was maintained at 180–250 s, during experiments; to ensure this condition, heparin was administered intravenously continuously; the infusion rate was 50 U/kg/h. Values of activated clotting times were monitored every hour using the Hemochron Junior + Microcoagulation System

(ITC, USA). Animals were orotracheal intubated, during experiments. A Hamilton G5 ventilator was used for mechanical ventilation (Hamilton Medical AG, Switzerland); the mode INTELLiVENT—Adaptive Support Ventilation was set. The mechanical ventilator was set to keep an oxygen saturation (SpO_2) of 95–99 %, and an end-tidal CO_2 pressure of 4.8–5.6 kPa [87, 86, 88].

4.1.2 ECMO system

Intubated animals underwent VA-ECMO implantation. For the purposes of experimental research Levitronix Centri-mag (Thoratec, USA); nonpulsatile centrifugal pump; tubing set with Quadrox membrane oxygenator with Softline Coating (MAQUET Cardiopulmonary AG, Germany); and a mechanical gas blender (Sechrist, USA) have been used. The peripheral cannulas were inserted into a femoral artery and femoral vein, after repeated dilatation, by using a standard Seldinger technique. Under ultrasound guidance, the larger diameter left or right femoral veins were used for venous cannula insertion. For the insertion of arterial cannulae, the same procedure for femoral artery selection was used. The tip of venous cannulas was positioned at the cava-right atrial junction; the position of the tip was verified using fluoroscopy. The sizes of the cannulas were 15 Fr for the arterial cannula, 23 Fr for the prototype of the DLAC, and 21 Fr for the venous cannula. Blood gases in the arterial site of the ECMO circuit (in the blood which living the oxygenator) were continuously detected by CDI^{TM} Blood Parameter Monitoring System 500, Terumo Cardiovascular Systems Corporation, USA) [87, 88, 93, 93]. The oxygen/air ratio and flow were adjusted, by the gas blender, to maintain pO_2 in the ranges of 10–15 kPa and pCO_2 in the ranges of 4.0–6.5 kPa in the blood which live the oxygenator. The extracorporeal flow was maintained at 1 L/min prior to the start of the measurements.

4.1.3 The double lumen arterial cannula prototype

The prototype of the DLAC (Figure 14) was fabricated from existing components, which are available on the market. The DLAC prototype was created by using a 23 Fr Avalon Elite double-lumen venous cannula (MAQUET Cardiopulmonary GmbH, Germany) (Figure 12) and of 10 Fr pigtail catheter (Cook Ireland Ltd., Ireland) (Figure 13).

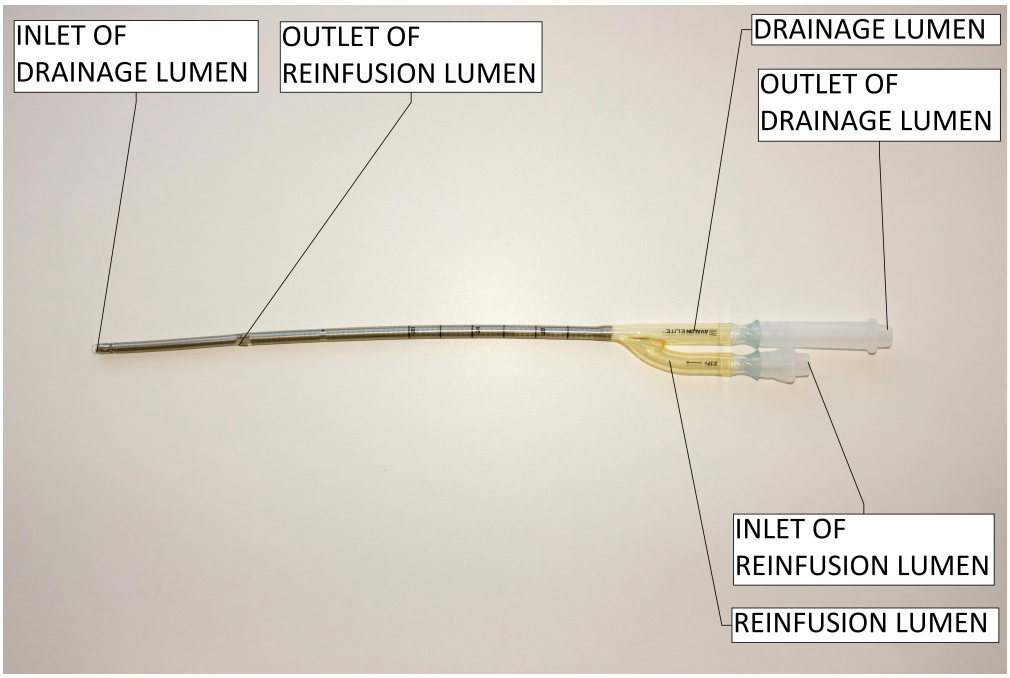


Figure 12: Avalon Elite double-lumen venous cannula

The 10 Fr pigtail catheter was inserted through the drainage lumen of a double-lumen venous cannula (Figure 15). The catheter was connected to the venous site of ECMO circuit by the connector with a lateral luer exit. The length of the pigtail catheter was 350 cm, therefore it was cut to 120 cm; this length is enough to reach from the insertion point (the femoral artery) to the LV in both the porcine mode and an adult person.

The reinfusion lumen of a double-lumen venous cannula served to return the oxygenated blood to the circulation, whereas the pigtail catheter, inserted through the drainage lumen of a double-lumen venous cannula, was used solely for LV unloading.

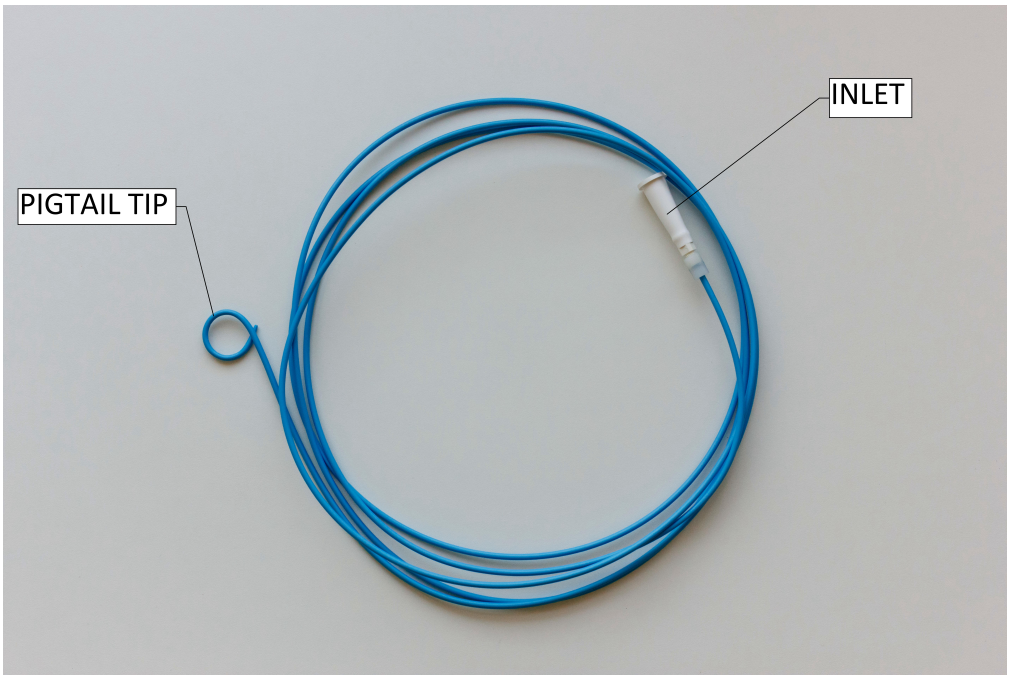


Figure 13: Pigtail catheter

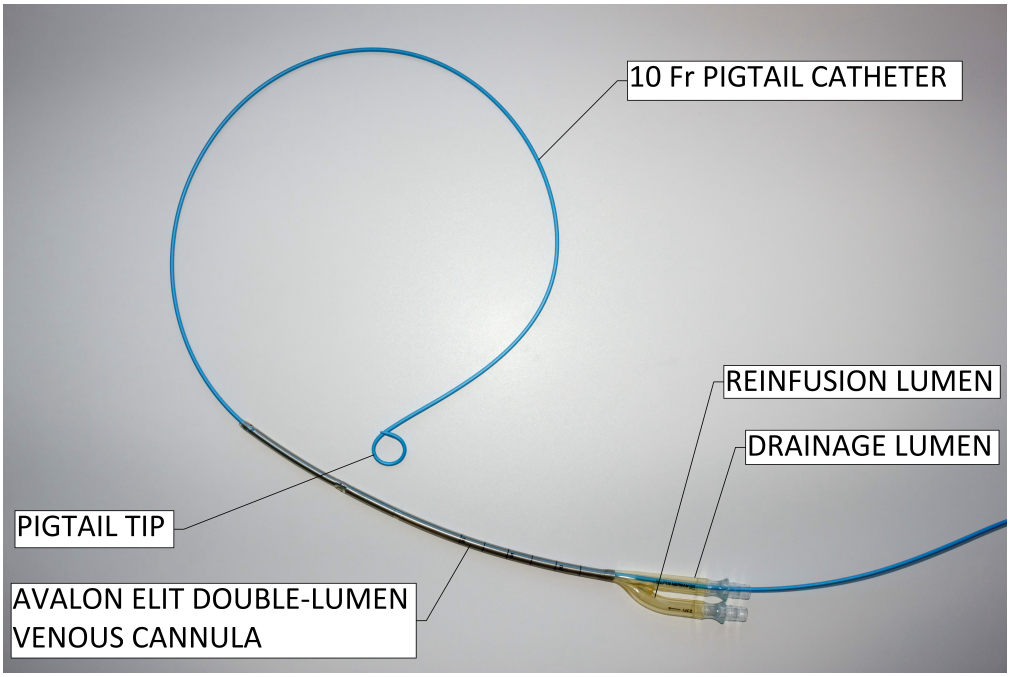


Figure 14: The prototype of double lumen arterial cannula

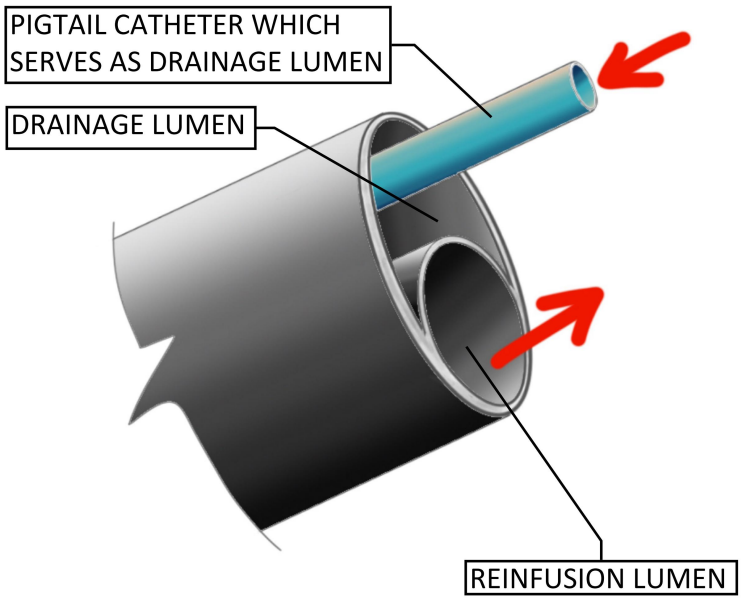


Figure 15: The embodiment of the double lumen arterial cannula prototype

4.1.4 The induction of cardiogenic shock

Induction of CS was attained within coronary arteries blood hypoxemia. The largest left main coronary artery branch (left anterior descending artery or left circumflex artery) was indicated in each animal; coronary angiography was used for this purpose. Then, guide wires were placed precisely in this vessel. The first guide wire was used for the introduction of a balloon catheter. The second guide wire was used for the introduction of an over-the-wire export catheter (Medtronic, USA). The tip of the over-the-wire export catheter was positioned distal to the end of a balloon. A proximal end of the export catheter was connected to the venous site of the ECMO circuit, between the ECMO pump end oxygenator (Figure 16). After inflation of the balloon in the vessel, the coronary artery branch was perfused via export catheter; the flow through catheter was approximately 40 ml/min. Since the largest left main coronary artery branch was perfused with venous blood, tissue hypoxia was achieved, and signs of CS were developed [87, 54]. CS in the studies was defined as a drop in SBP to <100 mmHg and at least one of the following criteria: increase in blood lactate to >2.0 mmol/L; decrease of SvO_2 to <50 %; or fall in brain tissue oxygen saturation to <50 %.

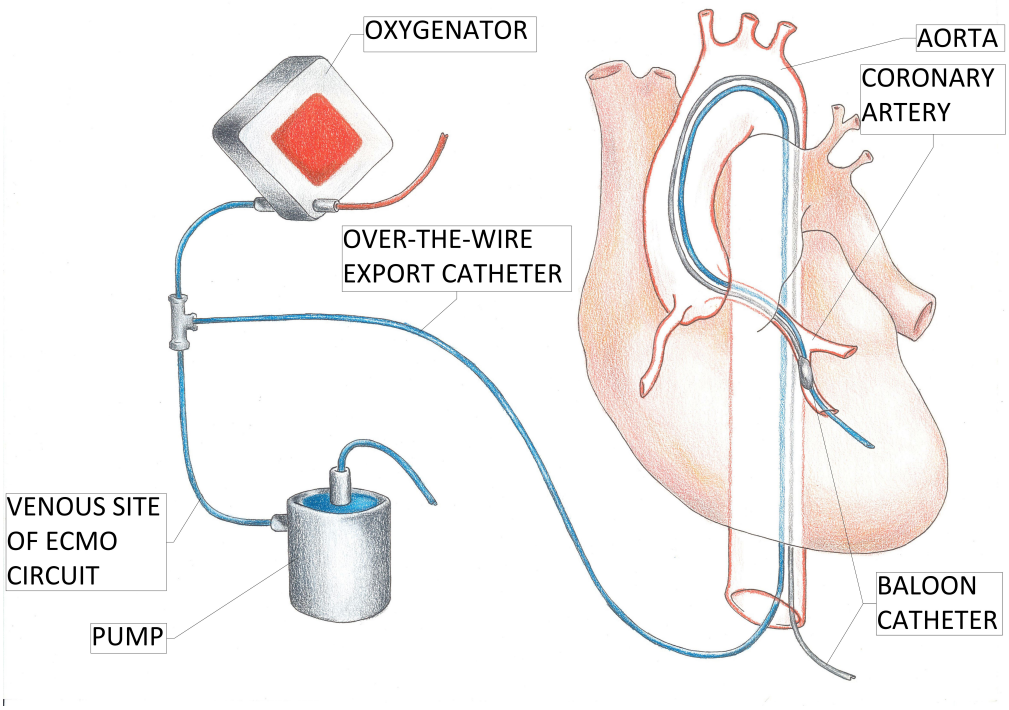


Figure 16: Initiation of regional cardiac hypoxia by perfusion with venous blood

If the above method did not cause signs of CS, the second balloon catheter was inserted into the periphery of the second left main coronary artery branch.

4.1.5 The vital functions and hemodynamic parameters

A standard invasive method was used for arterial pressure measurement; for this purpose a pigtail catheter and fluid-filled pressure transducers were applied (Truwave, Edwards Lifesciences, LLC, USA). A pigtail catheter was inserted into the aortic arch. Pulmonary cardiac output (pCO) was measured by a Swan–Ganz catheter; it was inserted via a femoral vein into the pulmonary artery. Invasive central venous oxygen saturation, HR, pulse oximetry, invasive blood pressures (aortic arch and jugular vein), capnometry, and electrocardiography were continuously monitored (Monitor Life Scope TR, Nihon Kohden, Japan; and Vigilance II, Edwards Lifesciences, USA). Near-infrared spectroscopy (INVOS Cerebral/Somatic Oximeter, Somanetics, USA) was used for measurement of brain oxygenation levels [87, 88, 93]. Pressure-volume (PV) analysis was achieved by using a PV conductance catheter (Scisense

7 Fr VSL Pigtail, Transonic, USA) which was connected to the PV unit (Sciense ADV 500, Transonic, USA). The PV catheter was operated in admittance mode; it was introduced, through the aortic valve, into the LV from the left carotid artery. Appropriate position of the PV catheter was assessed radiographically by confirming optimal PV loop morphology. The calibration of the volume was conducted against pulmonary thermodilution (Combo CCO catheter, Edwards Lifesciences, USA) at baseline. Cardiac performance was continuously monitored; PV data were recorded [87, 88, 93]. During the experiments values of SBP, end-diastolic pressure (EDP), end-systolic volume (ESV), end-diastolic volume (EDV), and value of stroke work (SW) were obtained (Table 2). The following parameters were calculated: SV = EDV−ESV; left ventricular ejection fraction (LVEF) LVEF = SV/EDV; left ventricular cardiac output ($_{\mathrm{LV}}$CO) $_{\mathrm{LV}}\mathrm{CO} = \mathrm{SV} * \mathrm{HR}$; recirculation minute volume (RecV) $\mathrm{RecV} = {}_{\mathrm{LV}}\mathrm{CO} - \mathrm{pCO}$; recirculation fraction (RecF) $\mathrm{RecF} = \mathrm{RecV}/{}_{\mathrm{LV}}\mathrm{CO}$.

4.1.6 Performing of the experiments conducted for the investigation of left ventricular performance parameters

First of all the catheters were inserted and ECMO was established. Then the animals were stabilized for 10 min. CS was induced and after achieving the signs of tissue hypoperfusion the animals were stabilized for 10 min. After stabilization the EBF was gradually increased by 1 L/min every 5 min to reach 5 L/min. When EBF 5 L/min was reached, EBF was decreased gradually every 5 min by 1 L/min. When EBF reached 1 L/min, the animals were stabilized for 10 min and the cycle of the measurement was repeated one more time [87]. The steps of the experiment are shown in Figure 17.

4.1.7 Performing of the pilot experiment with the double lumen arterial cannula

First of all the catheters were inserted and ECMO was established. CS was induced and after achieving the signs of tissue hypoperfusion the animal was stabilized for 10 min. Then the arterial cannula, which was inserted through the femoral artery, was replaced by a DLAC

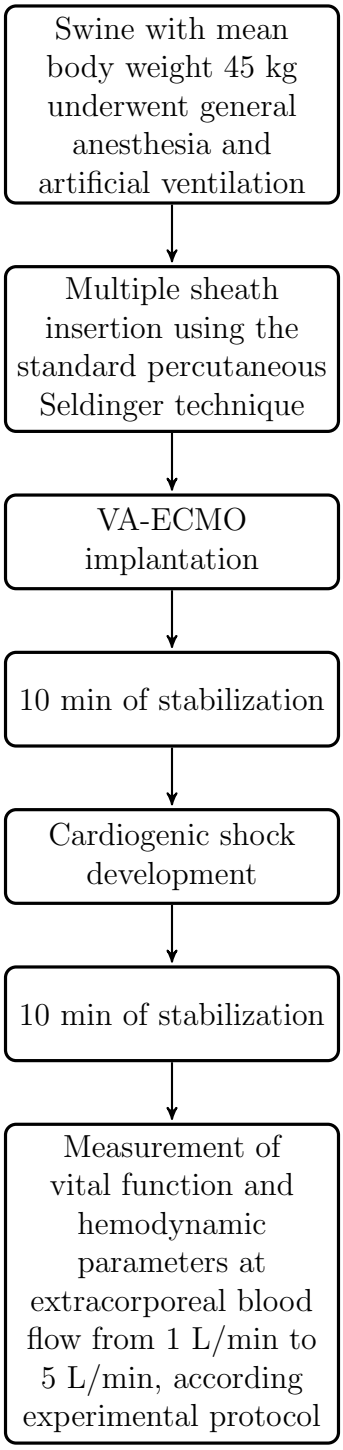


Figure 17: The steps of the experiment in a porcine model of cardiogenic shock under veno-arterial extracorporeal membrane oxygenation

prototype. The tip of the reinfusion lumen of the prototype of the DLAC was placed in the aorta. The tip of the drainage lumen of the prototype of the DLAC was inserted to LV, as depicted in Figure 18. Then animal was stabilized for 10 min. After stabilization of the

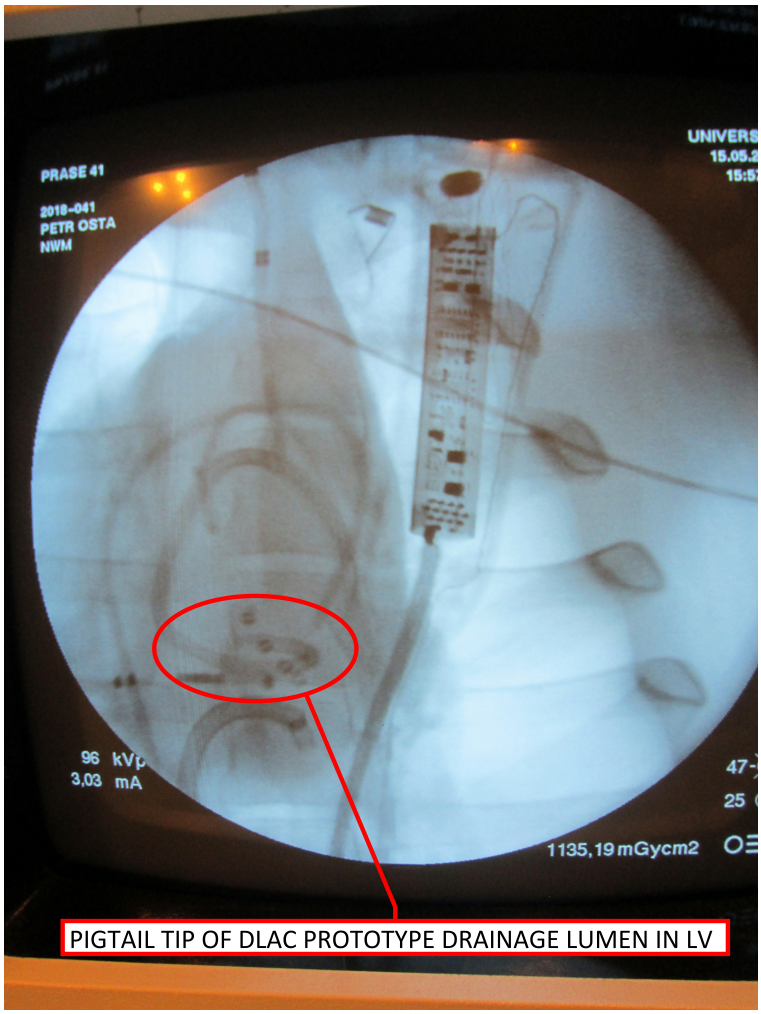


Figure 18: The tip of the drainage lumen of the double lumen arterial cannula prototype in the left ventricle

model of CS, the measurements of LV performance parameters were conducted. Primarily, the drainage lumen of the DLAC was clamped, and the DLAC operated as a simple arterial cannula; then, the clumped drainage lumen was unclamped and the cannula was used in full. The cycle of the measurement was repeated six times.

4.2 Drawing of the double lumen arterial cannula

The drafts of DLAC for ECMO was created in AutoCAD software. The drafts are presented in Figures 19, 26, 27, 35 and in the Appendices C, D. AutoCAD is a computer-aided, popular engineering design software program for creating engineering drafting, developed and marketed by Autodesk. It offers traditional 2D drawings as well as 3D drawing tools. The AutoCAD software interface is shown in Figure 19.

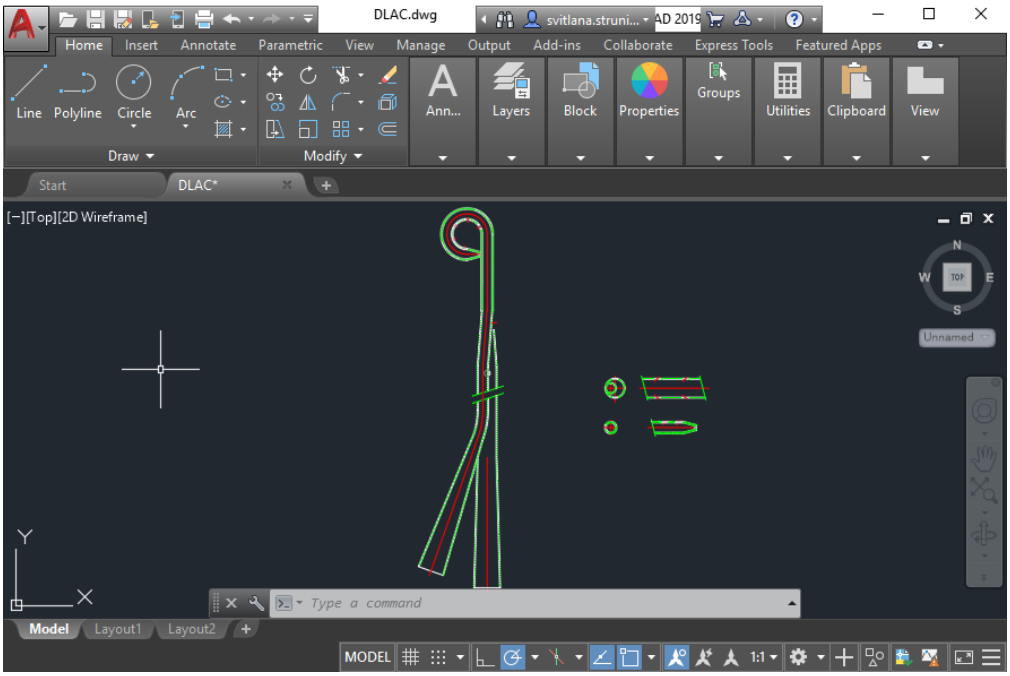


Figure 19: AutoCAD software interface

4.3 Modeling and simulation

4.3.1 The Modelica modeling language

To create the model, the Modelica modeling language (Modelica Association) in the Dymola (Dassault Systemes) modeling environment and components from Physiolibrary 2.3.1. were used. The Modelica language is an object-oriented, hierarchical, equation-based and acausal modeling language [109], in which models can be created and graphically represented from

pre-prepared components or by connecting instances of classes from libraries [33, 70, 46]. The Modelica interface is shown in Figure 20.

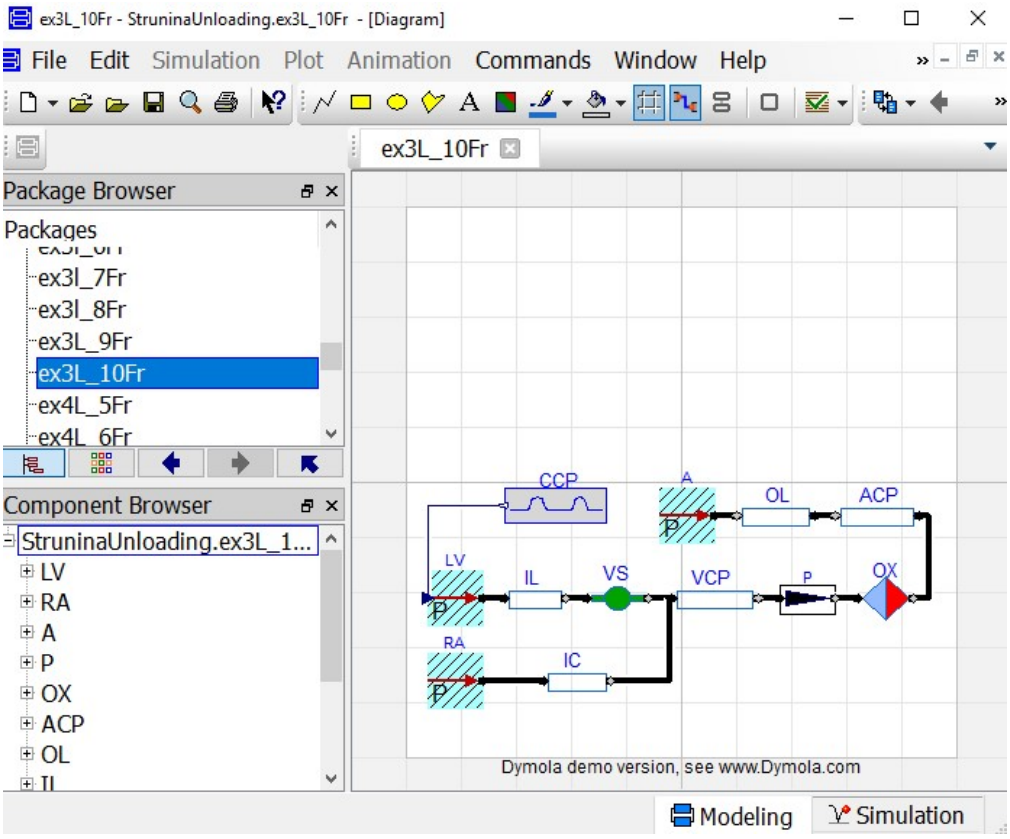


Figure 20: Modelica interface

Modelica is an acausal modeling language, which means that the equations that describe the behavior of the compartment can be expressed declaratively and the Modelica tool determines which of the variables are dependent and independent based on the context upon a compilation [53]. In the created models, in Modelica, it is enough to set up the set of parameters (if it needed), to start simulation [70]. Parameters in Modelica are the input data, which are constant with respect to time [115]. In the result of the simulation, the user can examine the change of variable values over time [70].

The main problem of medical research, articles, and experiments is using various units in medicine, in pharmacology, in biology, and in non-physics disciplines. One of the advantages of the Modelica environment is the support of non-SI units in the parameter dialog of each

component. Values are represented by SI-units in the text code, but the Modelica environment supports non-SI units in the parameter dialog of each component [109]. Physiological units are implemented as the displayUnits for each variable. Using displayUnits, the user can establish and observe the "physiological" values [69].

Furthermore, Modelica is a multidomain programming language. The user has the opportunity to describe and connect model parts from varying domains in the model; such as electrical, mechanical, thermodynamic, hydraulic, and biological domains. Modelica has a general class concept that unifies classes, generics, and general subtyping into a single language construct. This feature makes it easier to reuse components and aids in the development of the models. Finally, Modelica has strong software for designing and connecting components, meaning that this language is suitable for the architectural description of complex physical and software systems [33].

4.3.2 Model description

The numerical model was employed to identify the association between the DLAC drainage lumen size and the blood volume withdrawn from the LV during various EBF. After that, the impact of ECMO venous cannula sizes on blood volume withdrawn from the LV during various EBF was investigated. Consequently, the numerical model was employed to evaluate the effect of the drainage lumen size of a DLAC and ECMO venous cannula size on LV unloading during VA-ECMO, considering various EBF. Modelica code of the model is presented in Appendix E.

The required models of systemic circulation have been connected to models of the ECMO system which were created to correspond with it and are necessary for research. The whole created model consists of the following compartments: LV, right atrium, aorta, pump, tubing set with an oxygenator, venous cannula, and lumens of the DLAC. The block diagram representation of a system model is presented in Figure 21.

Each compartment is modeled using a mathematical relationship between blood volume $V_i(t)$, input flow rate $Fi_{in}(t)$ and output flow rate $Fi_{out}(t)$ relative to the i-th compartment

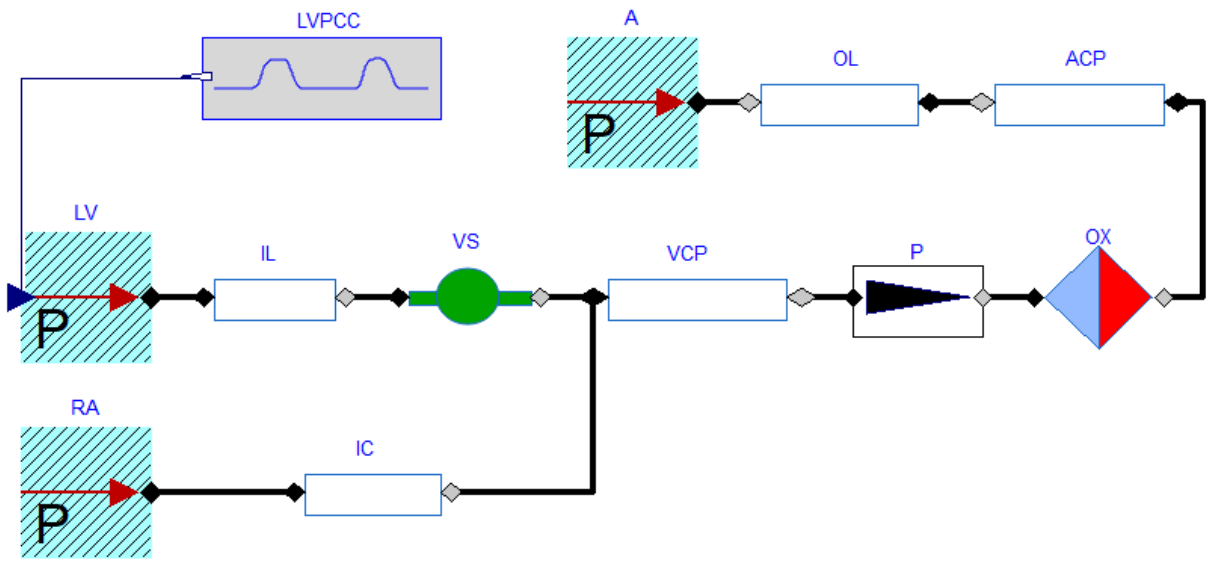


Figure 21: The block diagram representation of a system model. LVPCC - left ventricular pressures throughout cardiac cycle, A - aorta, OL – outflow lumen, ACP - arterial site of the ECMO circuit, LV - left ventricle, RA - right atrium, IL - drainage lumen, VS - volume sensor, VCP - venous site of the ECMO circuit, P - pump, OX - oxygenator, IC - inflow cannula

given as [28]

$$\frac{dV_i(t)}{dt} = F_{i_{in}}(j) - F_{i_{out}}(j) \tag{1}$$

with a flow rate $F_{ij}(t)$ between compartments i and j defined in general by [28]

$$F_{ij}(t) = \frac{P_i(t) - P_j(t)}{R_{ij}} \quad j = i - 1 \tag{2}$$

Analogous to Kirchhoff's current law, which is applied in the electrical domain, the law sum-to-zero is applied in the hydraulic domain to the flow variables. The sum of all mass flows at any given point is zero [33]

$$F_{in} - F_{out} = 0 \tag{3}$$

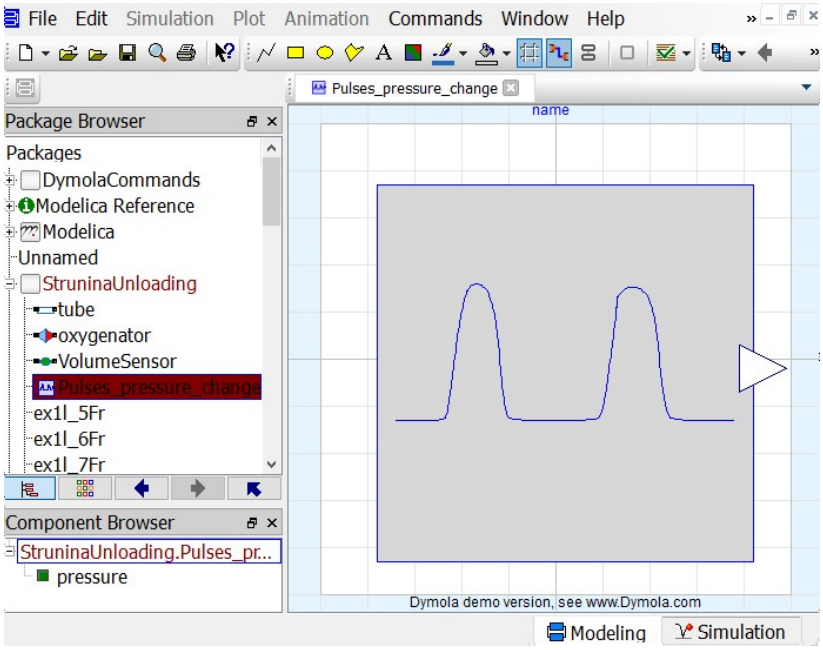
Left ventricular pressure

The LV pressures were established according to a single cycle of cardiac activity time given as in equation (4). The equation from Kulhanek et al. [53] for changing the flow, in the heart chamber, was modified and adjusted for the expression of pressure in the LV [109]. The Figure 22 depicts LV pressures compartment in the Modelica language interface. The parameters were set in accordance with the data obtained from experiments with a large animal model of CS.

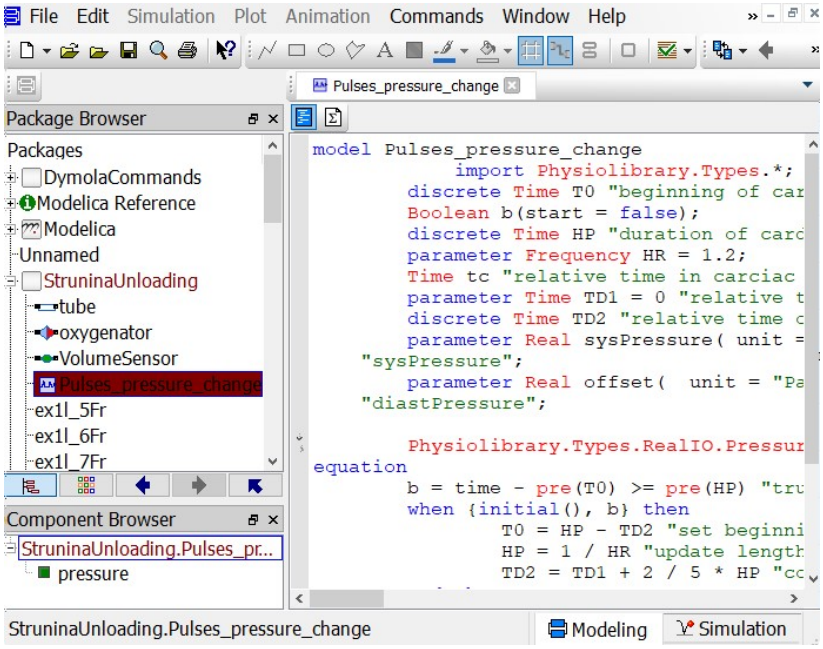
$$pressure = \begin{cases} diaPressure & if\ tc < TD1 \\ diaPressure + \sin\left(\frac{tc-TD1}{TD2-TD1}\pi\right)(sysPressure - diaPressure) & if\ tc < TD2 \\ diaPressure & else \end{cases} \quad (4)$$

Circuit

The circuit of the ECMO refers to the disposable tubing that forms the path that the blood follows. The perfusionist is responsible for designing a circuit that meets the requirements; that depends on many factors. Perfusion circuits vary from institution to institution, but there are components common to all circuits [60]. The size of the ECMO circuit venous site was set at 1/2 inch (1,27 cm) in the model. The size of the ECMO circuit arterial site was set at 3/8 inch (0,95 cm). In the ECMO model, the standard arterial cannula was replaced by a DLAC. The DLAC consists of two lumens, the shorter and the longer one. The shorter lumen of the DLAC serves as a blood reinfusion lumen. The end of the shorter lumen is positioned in the aorta. The cross-sectional area of the reinfusion lumen fits the size of the 15 Fr peripheral cannula. The length of the reinfusion lumen was set to 60 cm. The longer lumen of the DLAC, the end of which is introduced into the LV and serves as a blood drainage lumen was, gradually increased from 5 Fr to 10 Fr. The length of the drainage lumen was set to 120 cm. The size of the venous inflow cannula was chosen to be 21 Fr, during the determination of the impact of drainage lumen size and extracorporeal blood flow on DLAC unloading capacities; which is the same as in the experimental study with large animal models with CS. The sizes of venous inflow cannulas were from 18 Fr to 29 Fr during



(a)



(b)

Figure 22: Left ventricular pressures compartment in the Modelica language interface a) left ventricular pressures compartment diagram b) left ventricular pressures compartment programming code

the determination of the impact of venous cannula size on DLAC unloading capacities. The length of the venous inflow cannula was set to 55 cm. The drainage lumen of the DLAC and the venous inflow cannula were connected to the venous site of the ECMO circuit by a Y shaped connector. The blood flows into the model compartments were described by the Hagen–Poiseuille equation. The equation brings together all of the variables that determine a flow

$$Q = \frac{\pi \Delta P r^4}{8 \mu L} \tag{5}$$

The Hagen–Poiseuille equation states that the maximum flow is inversely proportional to the lumen length and directly proportional to the fourth power of the radius for a circular cross-section of the lumen [51]. The dynamic viscosity of blood 0.001 Pa·s was chosen [116]. The Figure 23 depicts the circuit compartment in the Modelica language interface.

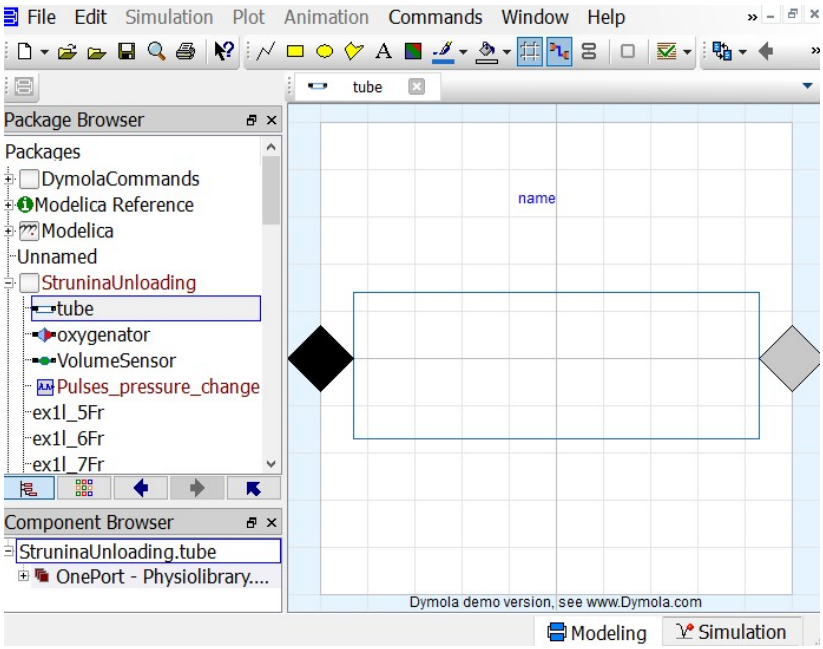
Oxygenator

The oxygenator was modeled as a compartment with a pressure gradient [109].

$$\Delta P = P_{in} - P_{out} \tag{6}$$

The value of pressure gradient per liter flow remains relatively constant during extracorporeal circulation, and the only difference between different types of oxygenators is the absolute values obtained. Fisher et al. report the measurements in various manufacturers' oxygenators. In conclusion, there were no statistically relevant differences in the pressure gradient at any timepoint during any bypass [30].

The Quadrox-i Adult oxygenator is a low-resistance, high-compliance oxygenator [119]. The parameters of adult hollow fiber membrane oxygenator Quadrox-i (Maquet Cardiopulmonary AG) were used for the oxygenator submodel in the created model. The value for mean pressure gradient per liter of Quadrox-i oxygenator is 10 mmHg [67]. The Figure 24 depicts the oxygenator compartment in the Modelica modeling language.



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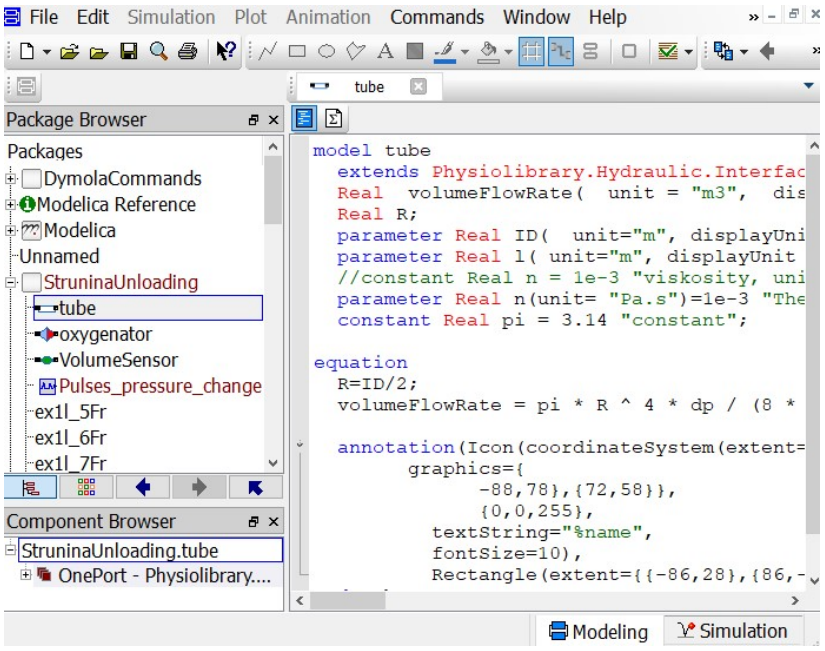

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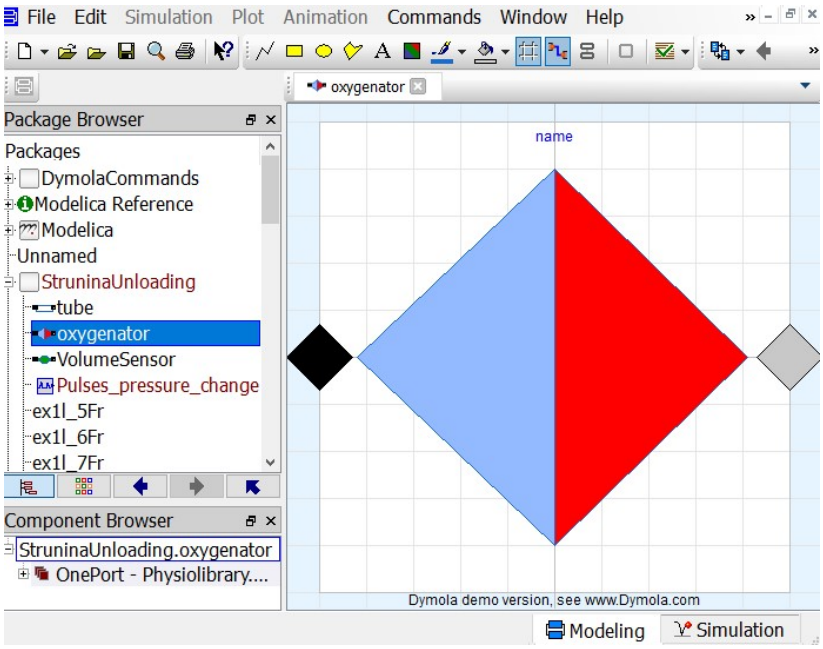
Figure 23: The circuit compartment in the Modelica language interface a) circuit compartment diagram b) circuit compartment programming code

Pump

The pump, in the ECMO system, supports or replaces the functions of the failing heart; it



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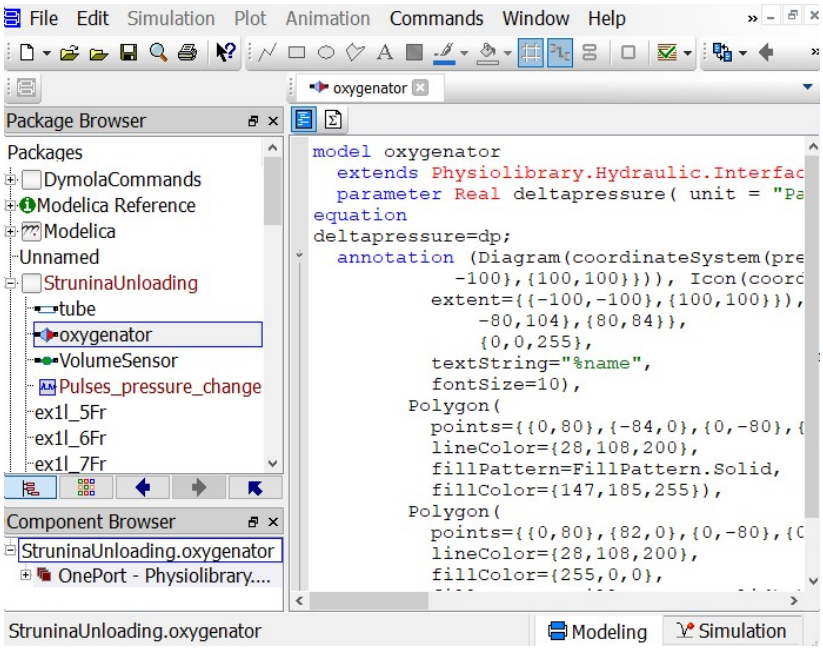


(b)

Figure 24: The oxygenator compartment in the Modelica language interface a) oxygenator compartment diagram b) oxygenator compartment programming code

provides circulatory support [109]. The pump propels the blood throughout the body [60] and the ECMO circuit. Required EBF can be easily set by the perfusionist and changed in case it

is needed. The contemporary ECLS circuits include a magnetically levitated centrifugal pump [95, 57]. The pump element was used from Modelica library for physiological calculations - Physiolibrary 2.3.1 [110]. The flow rates of the model pump were setting at 1 L/min, 2 L/min, 3 L/min, 4 L/min, and 5 L/min for each tested size of DLAC drainage lumen, and ECMO venous cannulas size. The Figure 25 depicts the pump compartment in the Modelica language interface.

4.3.3 Parameters of the cardiovascular compartments

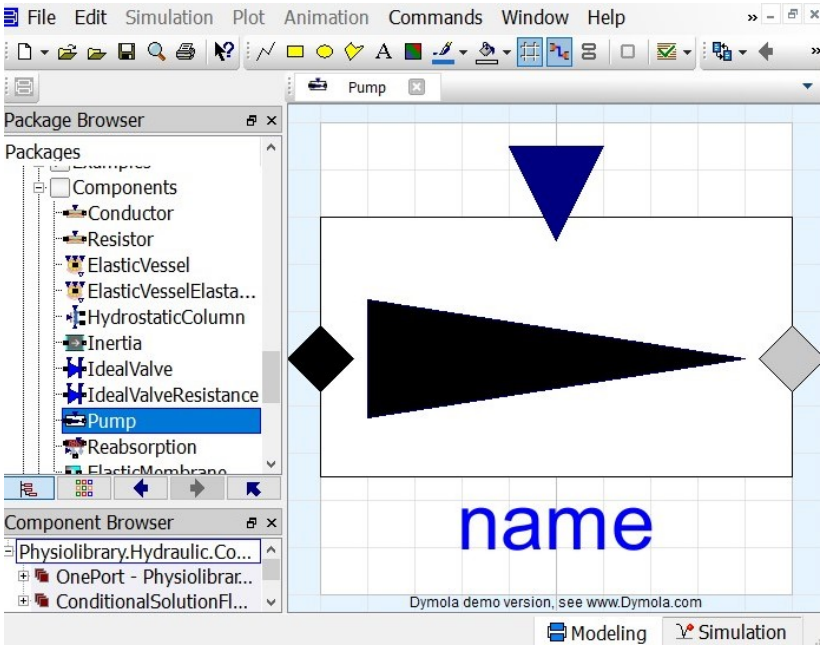
In the Modelica modeling language, the keyword "parameter" specifies that the quantity is constant during a simulation run, but values can be changed between runs. A parameter is a quantity that simplifies changing the behavior of a model by a user [26]. The parameters of cardiovascular compartments, in the model, were obtained from a standard in vivo experiment on a porcine model of CS. The parameter values of LV hemodynamic parameters were derived from measurements described above. The selected LV performance parameters of a porcine model of CS, which were used in the computer model, are presented in Table 1.

Table 1: The values of the model parameters

Extracorporeal blood flow	1 L/min	2 L/min	3 L/min	4 L/min	5 L/min
End-systolic volume [ml]	64	70	74	78	83
Systolic blood pressure [mmHg]	60	72	81	89	97
LV end-diastolic pressure [mmHg]	17.2	18.2	18.6	18.9	19
Heart rate [bpm]	94	89	84	80	77

4.3.4 The protocol of simulations

For the purpose of the simulation, the pump volume flow rate was gradually increased from 1 L/min to 5 L/min. For each value of the extracorporeal blood flow the value of SBP, LV EDP, HR were changed in accordance with obtained data from an experiment on a porcine



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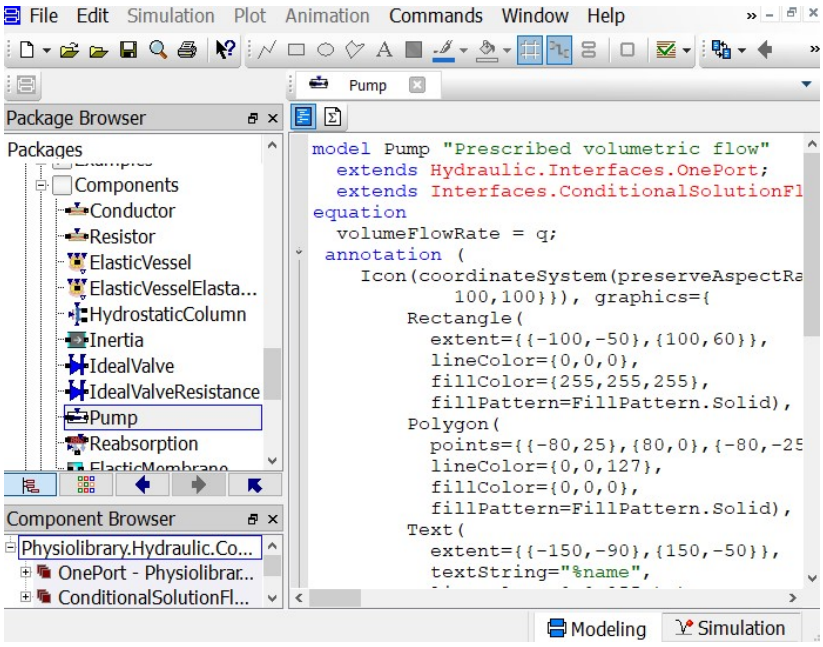


(b)

Figure 25: The pump compartment in the Modelica language interface a) pump compartment diagram b) pump compartment programing code

model of CS (Table 1). The internal diameter of the drainage lumen of the DLAC was gradually increased from 5 Fr to 10 Fr for each EBF value [109]. The internal diameter of

the venous cannula was gradually increased from 18 Fr to 29 Fr for each drainage lumen of DLAC sizes. The entire process was done for each unique combination of the pump flow, drainage lumen size of the DLAC, peripheral venous cannula, and vital parameters which were achieved from the porcine model of CS.

4.4 Statistical analysis

The data obtained from experiments with a porcine model of CS with a standard arterial cannula during various EBF were analyzed by using GraphPad Prism 5.0 software (GraphPad, USA). A repeated-measures one-way ANOVA with Tukey's multiple comparison test, or a Friedman test with Dunn's multiple comparison test (for data sets without normal distribution) was used. The level for P value less than 0.05 was considered to be statistically significant. To estimate the significant difference between selected hemodynamic parameters in a porcine model of CS during EBF from 2 L/min to 5 L/min compared with value at EBF 1 L/min, the following clinical variables were tested: the SBP, EDP, ESV, EDV, SW, SV, LVEF, CO, RecV, and RecF [87].

For the statistical analysis of the data, which were achieved during the pilot experiment with the animal model of CS, the data were downloaded into R 3.5.3 for Windows (The R Foundation, Vienna, Austria). R is a freely available language and environment for statistical computation and graphics [118]. The box plots used to display a box that contains the interquartile range with a line signifying the median, the whiskers (dashed line) cover 1.5 times the interquartile range. The collected data that approximated a normal distribution were reported as mean ± the standard error of the mean and were tested for differences by the two-sample t-test. The collected data that did not approximate a normal distribution were reported as a median ± standard error of the median and were analyzed by the Wilcoxon rank-sum test (Mann-Whitney U test). Standard errors of the median were computed by using a bootstrap approach. To estimate the significant difference between LV performance during VA-ECMO with using a standard arterial cannula and LV performance

during VA-ECMO with using DLAC, the following clinical variables were tested: arterial diastolic pressure (ArtD), SBP, EDP, ESV, LVEF, EDV, SV, LV contractility (dP/dt). The cut-off level for a P value of 0.05 or lower, which is the same as in the previous experiments, was considered statistically significant.

5 Results and discussion

The purpose of this chapter is to depict an experimental study with a porcine model of CS under VA-ECMO and the effect of ECMO therapy on LV performance; to present an alternative method of LV unloading or LV overload reduction, which has the potential for reducing the invasiveness of LV unloading during VA-ECMO therapy using a novel DLAC; further, to describe DLAC parameters and features. Thereafter, to describe numerical modeling and simulation to identify the association between both the drainage lumen size of the DLAC and achieving LV decompression during ECMO therapy, and venous cannula size and achieving LV decompression during ECMO therapy. The last part of the chapter depicts the pilot study with a porcine model of CS under VA-ECMO, using DLAC instead of a standard arterial cannula, to investigate the ability of DLAC to decompress LV during ECMO.

5.1 Left ventricular performance parameters in a porcine model of CS under VA-ECMO

The aim of the experiment was to research and establish the impact of the VA-ECMO therapy on the LV performance parameters in a porcine model of a CS. Collected data, during the experiment, were then used for further modeling and simulation. The results of modeling and simulation are described in the following paragraphs.

The measured data, during the experiment, and calculated data of vital functions and hemodynamic parameters are listed in Table 2. The results of experimental studies indicated that as a result of application of VA-ECMO, and with increasing EBF in the failing heart, SBP is increased ($P < 0.001$) and HR is decreased ($P < 0.001$); these changes tended toward the normal values. Furthermore, with increasing EBF and SBP, increasing in ESV ($P < 0.001$), decreasing in SV ($P = 0.045$), decreasing in LVEF ($P < 0.001$) were observed; and as a consequence, CO is decreased ($P < 0.001$). Although, EDV ($P = 0.43$) and EDP ($P = 0.87$) values increased numerically with increasing EBF; nonetheless, these differences did not reach sta-

Table 2: Collected data from experimental studies with the porcine model of cardiogenic shock. EDP - end-diastolic pressure; EDV - end-diastolic volume; SBP - systolic blood pressure; ESV - end-systolic volume; SW - stroke work; HR - heart rate; SV - SV; LVEF - left ventricular ejection fraction; LVCO - left ventricular cardiac output. Results are expressed as mean ± SEM

Extracorporeal blood flow	1 L/min	2 L/min	3 L/min	4 L/min	5 L/min	P value
EDP [mmHg]	17.2±1.4	18.2±0.7	18.6±1.5	18.9±2.4	19.0±2.9	0.87
EDV [ml]	112±19	115±19	116±19	119±19	123±20	0.43
SBP [mmHg]	60±7	72±7	81±6	89±7	97±8	< 0.001
ESV [ml]	64±11	70±11	74±11	78±12	83±14	< 0.001
SW [mmHg·ml]	2096±342	2510±335	2752±346	3031±404	2884±412	< 0.001
HR [bpm]	94±4	89±3	84±3	80±2	77±2	< 0.001
SV [ml]	48±9	45±9	42±9	41±9	40±8	0.045
LVEF [%]	43±3	39±2	36±3	34±3	32±3	< 0.001
LVCO [L/min]	4.31±0.40	3.90±0.47	3.49±0.51	3.21±0.40	2.99±0.38	< 0.001

tistical significance. However, EDV and EDP were notably affected not only by afterload but also by preload. Also, the elevation of SW ($P < 0.001$) with increased EBF was observed [87].

An experimental study in a porcine model confirmed the undesirable negative effects of VA-ECMO on LV performance parameters in flow dependent manner; with increasing EBF the left heart performance deterioration was observed in the model of CS. The results of the conducted study correspond with numerous other studies [40, 48, 16, 94, 47, 34, 106, 13]. As was mentioned in Chapter 2, numerous studies focused on the requirement to unload LV during VA-ECMO; insufficient LV unloading can lead to LV distention and severe pulmonary edema [8], which is often observed in patients with a severely depressed LV function on high-flow VA-ECMO. Conducted experimental studies indicate deterioration of LV function as a result of increasing EBF. The appropriate way to prevent complications such as LV overload, caused by VA-ECMO, is applying low flow ECMO. However, a low flow ECMO is

frequently not sufficient to achieve adequate end-organ tissue perfusion during extracorporeal circulatory support. Despite the fact that a nonpulsatile centrifugal ECMO pump meets the requirements of most institutions at the present time, nonpulsatile extracorporeal flow has to maintain at least 20 % or 30 % higher flows than generally utilized for pulsatile flow, to correct the abnormal physiology tends by itself [121]. The blood flow through the aorta of a 70-kg man at rest is about 5 L/min [105], accordingly, 7 L/min nonpulsatile flow for a 70-kg person is recommended [121]. Thereby, mostly it is impossible to achieve adequate tissue perfusion with low flow ECMO, and LV unloading is a necessary, required procedure during VA-ECMO support. A number of methods have been suggested to deal with LV unloading during VA-ECMO; however, each of the current methods require extra intervention and increase invasiveness [110], which can lead to additional complications and can prolong patient recovery time. An alternative method, of LV unloading, is the application of a novel DLAC during VA-ECMO therapy. DLAC might provide a great opportunity to unload LV and reinfuse the oxygenated blood to the circulation by one single cannula. Using DLAC could be considered a less-invasive method than currently existing methods for decompressing LV of the patient under VA-ECMO.

5.2 Double lumen arterial cannula for VA-ECMO

A known manner of performing VV-ECMO and hemodialysis utilizes is a single cannula in which blood is both extracted and returned through the same cannula. Over the past years, the double-lumen cannulas were widespread in the VV-ECMO therapy. This type of cannula is less-invasive, reduces the circuit size and minimizes interaction between blood cells and the circuit [51]. The DLAC is the novel variation of double lumen cannula. The DLAC is a patented invention: Strunina, S.; Hozman, J.; Ošťádal, P. A cannula containing a base tube with two adjacent longitudinally leading lumens. Czech Technical University in Prague, Faculty of Biomedical Engineering. Czech Republic. Patent. CZ 307196. 2018 - 01 - 31. The patent document is presented in Appendix B. The object of the invention is to provide a

DLAC for VA-ECMO which could be capable of achieving LV decompression and can reinfuse the oxygenated blood with only one cannula, consequently only one puncture. Drafting of DLAC for VA-ECMO in AutoCad environment is depicted in Figure 26.

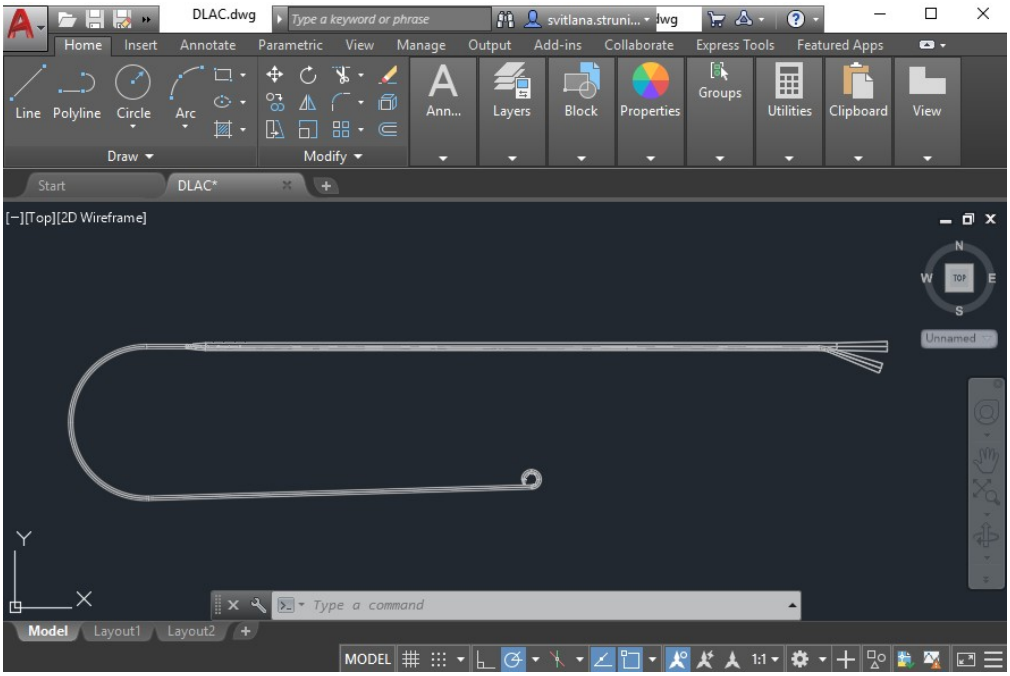


Figure 26: Double lumen arterial cannula for veno-arterial extracorporeal membrane oxygenation in AutoCad environment

5.2.1 Summary of the invention

The novel DLAC for VA-ECMO (Figure 27) relates to surgical instruments. The DLAC is a flexible one-piece cannula; the cannula is reinforced. This configuration decreases hemolysis and prevents kinking or collapse of the cannula. A DLAC serves for reinfusion of oxygenated blood and LV unloading during VA-ECMO. The present invention consists of a single arterial cannula having two contiguous lumens, one is longer than the other. The shorter lumen, the end of which is positioned in the aorta, serves as a blood reinfusion lumen. The longer lumen, the end of which is introduced into the LV, serves as a blood drainage lumen [110]. With this arrangement, oxygenated blood is reinfused to the aorta and LV is unloaded by one single cannula. The aforementioned cannula does not require further intervention to

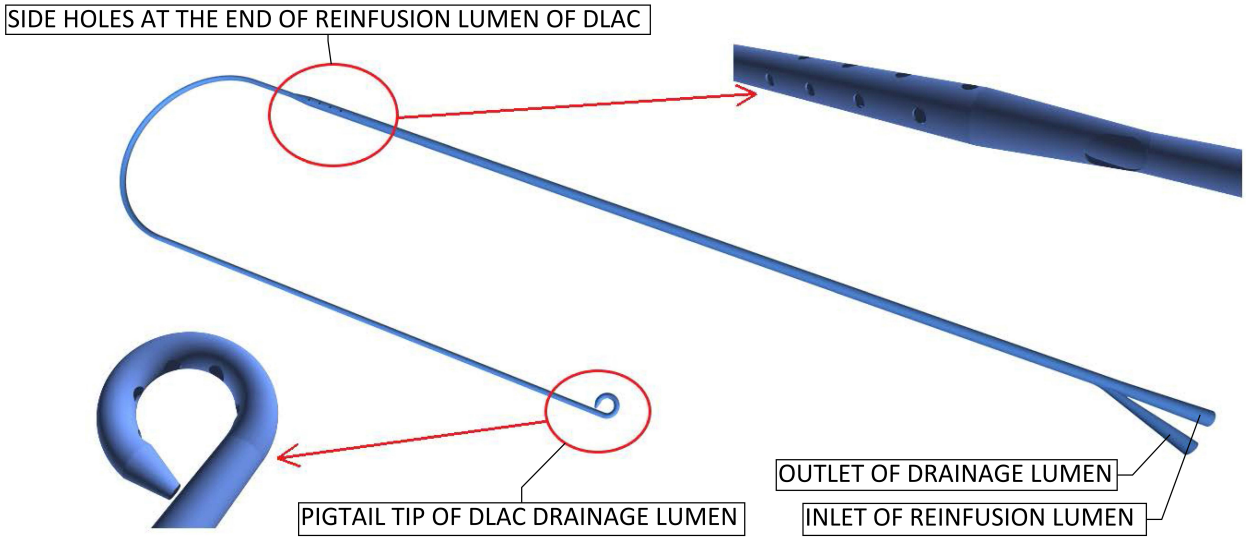


Figure 27: Drafting of the double lumen arterial cannula

achieve LV unloading during VA-ECMO as currently used methods for LV unloading during VA-ECMO do. Under these circumstances, the risk of additional complications, caused by further interventions, such as infection, bleeding and longer recovery time could be prevented.

The DLAC is inserted percutaneously over the guide wire, using the standard Seldinger technique. It was shown that, using the Seldinger technique for the placement of femoral venous cannulas in adult and pediatric patients results in fewer bleeding complications, less costly cannulation procedures, and less complicated decannulations [96].

Seldinger's technique sequence includes needle puncture, a guidewire through the needle, removal of the needle; then inserting the vessel dilator over the guidewire into the vessel, removal of the vessel dilator, threading of the cannula over a guidewire, and the removal of the guidewire. A guidewire, which is used during Seldinger's technique, is a flexible, round-ended, metal leader [39]. An elongated lumen of DLAC, which is a drainage lumen, is inserted to the LV through the femoral artery then through the aorta and aortic valve (AV). The drainage lumen of DLAC has a pigtail tip. The pigtail tip serves to prevent the wall of the heart chamber from being drawn to the catheter tip [110]. The drainage lumen of the DLAC is connected by a Y connector to the venous site of the ECMO circuit; where a centrifugal pump withdraws the blood from the right atrium and, in case of using DLAC,

from the LV. Both drainage and reinfusion lumens of the DLAC have multiple side holes at the tips. The side holes decrease mechanical stress on blood components [51], and increasing the number of side holes generally reduces the mechanical stress on blood cells [90].

Park et al. reported that the angle of cannula side holes has a significant effect on the flow pattern. In the Park et al. study, the side hole angles 0°, 15°, 30°, and 45° were investigated. The angle represents the rotation of the hole from its original vertical position. A smoother flow pattern occurs when the angle of cannula side holes increases, in addition an increase in cannula side holes results in higher flow rate. Park indicated that a cannula with a 45° angle of the side holes allows a higher flow rate and greater reduction of shear rate than cannulas with 0°, 15°, 30° side hole angles [90]. Accordingly the angles of DLAC side holes are 45° (Appendix D).

The catheters for the peripheral LV catheterization which are inserted in the femoral artery must be approximately 120 cm long, in order to reach from the insertion point to LV. Accordingly, the entire length of the cannula would be more than 120 cm (Appendix D). The blood reinfusion lumen, which returns the oxygenated blood to the circulation, is about 60 cm length (Appendix D). The length of the drainage lumen, which withdraws the blood from LV for unloading of LV during VA-ECMO, is about 120 cm (Appendix D).

The inserted length of the cannula can be changed according to requirements. Therefore, the DLAC is suitable for patients with different anatomical features and parameters.

The radiopaque markers, located in the DLAC distal end, are used to denote the location of the distal end.

5.2.2 Description of the preferred embodiment

The DLAC in accordance with the present invention is designed for LV unloading and reinfusion of the oxygenated blood to the patient‘s circulatory system during VA-ECMO. Appendix C presents the drawings for the description of the preferred embodiment.

Referring to Figure 1 in Appendix C it can be seen that the present invention consists

of a single arterial cannula (1), comprising an elongated tubing (2), has two longitudinally spaced lumens (3 and 4). The lumens are separated.

Figure 1 in Appendix C is a side cross-sectional view of a cannula in accordance with the present invention.

The drainage lumen (4) of the DLAC, which extends from the proximal end of the cannula to the distal end (6) of the cannula, is terminated by one or more side holes or perforations (7) at the distal end of the lumen. The drainage lumen (4) size is about 10 Fr (3.3 mm) in diameter. Figure 3 in Appendix C is a transverse cross-sectional view of a lumen (4) in accordance with the present invention, shown along line B-B.

The reinfusion lumen (3) of the DLAC, which leads from the proximal end (18) of the cannula to the position of the reinfusion lumen end (8), is terminated by one or more side holes or perforations (9).

Figure 2 in Appendix C shows a cross-sectional view of a cannula in accordance with the present invention, shown along line A-A.

Side holes or perforations (7) at the distal end of the drainage lumen extends beyond the side holes or perforations (9) at the end of the reinfusion lumen by 60 centimeters. The distal end of the drainage lumen (4) is inserted into the LV. The end of the reinfusion lumen (3) locates in the aorta.

The inserted length of the cannula, the separation "12" would be approximately 120 cm. The separation "13" on Figure 1 in Appendix C would be approximately 60 cm. The non-inserted ends of the lumens are connected to the ECMO circuit. This connection can be accomplished by separating the lumens 3, 4 into two noncontiguous tubes (10, 11) of circular cross-section. The length of the connecting tubes 10, 11, the separations "14, 15" would be approximately 7 cm.

The distal end of the drainage lumen (2) has a pigtail tip, which can be straightened by the passage of a guidewire to allow the pigtail to be passed through the aortic valve into the LV. The guide wire is then withdrawn, leaving the pigtail catheter in the LV, so that the

pigtail resumes its shape in the LV.

The proximal ends of lumens 16 and 17 are adapted to attach to the ECMO circuit by connecting with standard 3/8 inch (9.52 mm) connectors.

A suitable material for the cannula (1) is Teflon (polytetrafluoroethylene) or polyurethane.

Manufacturing drawings of DLAC are presented in Appendix D.

5.3 Double lumen arterial cannula capacities for left ventricular overload reduction during VA-ECMO therapy

The LV decompression is associated with a significant improvement of the LV function during the VA-ECMO therapy [25]. As was mentioned before, an alternative method to prevent LV overload during VA-ECMO is the application of the novel DLAC. As outlined earlier, DLAC is a peripheral, flexible, dual lumen cannula. The first lumen is longer and the second lumen is shorter. The longer lumen serves for LV decompression; the tip of the longer lumen introduced into the LV through the aortic valve and serves as a blood drainage lumen. The drainage lumen (the longer lumen) of the DLAC is connected to the venous side of the ECMO circuit by a Y-shaped connector and the blood is withdrawn by the centrifugal pump from the LV (Figure 28). The shorter lumen of DLAC, the outflow lumen, serves to reinfuse into the aorta blood that has been oxygenated in the oxygenator. Thereby, oxygenated blood returns to the aorta and LV is unloaded by one single cannula which requires only one puncture [110]. The effect on LV decompression of the diameter of the drainage lumen of the DLAC and the EBF value were investigated using modeling and simulation. The main objective of the simulation study was to assess the unloading capacities of various diameters of the DLAC drainage lumen during various EBF values, and various venous cannula sizes.

The Modelica modelling language was employed 1) to identify the associations between DLAC drainage lumen diameter and volume value withdrawn from the LV during ECMO; 2) to identify the associations between EBF value and volume value withdrawn from the LV by the drainage lumen of DLAC; 3) to identify the associations between venous cannula size

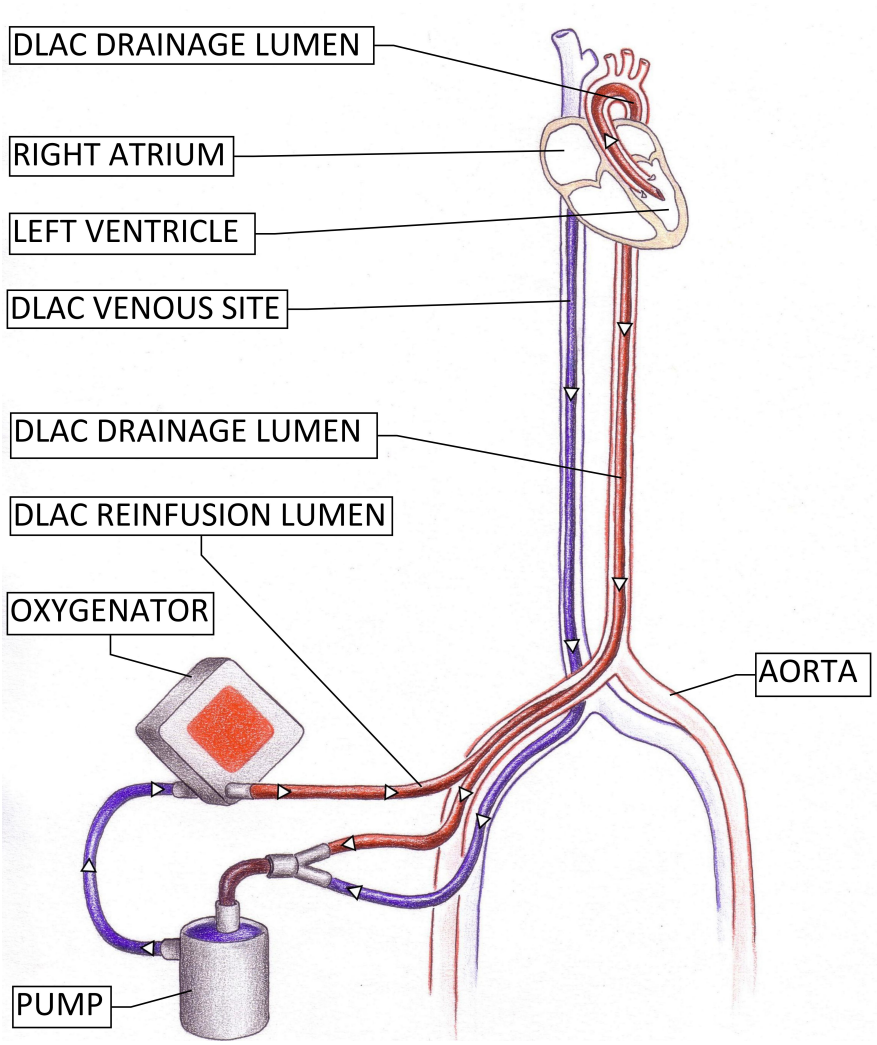


Figure 28: Left ventricular unloading by the double lumen arterial cannula during veno-arterial extracorporeal membrane oxygenation

and volume value withdrawn from the LV by the drainage lumen of DLAC. Consequently, to evaluate the effect of the drainage lumen diameter, EBF, and venous cannula size on the LV unloading. The data of hemodynamic and cardiac performance parameters, which were obtained from the experimental studies with the porcine model of CS on VA-ECMO, were used for creating the model.

5.3.1 Impact of drainage lumen size and extracorporeal blood flow on DLAC unloading capacities

The outcomes of the simulation on the created model have estimated that 5 Fr drainage lumen of DLAC withdraws from 0.23 ml to 0.41 ml for the cardiac cycle during EBF from 1 L/min to 5 L/min; 6 Fr drainage lumen of DLAC withdraws from 0.48 ml to 0.85 ml for the cardiac cycle during EBF from 1 L/min to 5 L/min; 7 Fr drainage lumen withdraws from 0.88 ml to 1.57 ml for the cardiac cycle during EBF from 1 L/min to 5 L/min; 8 Fr drainage lumen withdraws from 1.5 ml to 2.69 ml for the cardiac cycle during EBF from 1 L/min to 5 L/min; 9 Fr drainage lumen withdraws from 2.38 ml to 4.26 ml for the cardiac cycle during EBF from 1 L/min to 5 L/min; 10 Fr drainage lumen withdraws from 3.59 ml to 6.42 ml for the cardiac cycle during EBF from 1 L/min to 5 L/min. Table 3 presents the results of the simulations.

The flow rate value through the drainage lumen throughout the cardiac cycles is not constant; the flow rate is varied throughout the cardiac cycles. Figure 29 depicts flow rate profiles of the blood throughout the cardiac cycles, which is withdrawn from LV by drainage lumen of the DLAC, according to drainage lumen size. The main point of this paragraph is the determination of the withdrawal volume amount from LV by drainage lumen of the DLAC for the one cardiac cycle. Figure 29 depicts the variation with time of the volume value withdrawn from LV by drainage lumen of the DLAC according to drainage lumen size; the red circles on Figure 29 depict volume values withdrawn from LV for one cardiac cycle.

Figure 30 depicts the simulation results of the variation with time of withdrawal volume values from left ventricle by various sizes of DLAC drainage lumen in the Modelica interface for one cardiac cycle. Figure 31 depicts withdrawal volume values for a cardiac cycle according to the drainage lumen size. The relationship between the withdrawal volume value for a cardiac cycle and the EBF is shown in Figure 32.

Computer simulation/mathematical modeling can provide relevant mechanistic insights and enhance our pathophysiological understanding of complex ECMO configurations aims

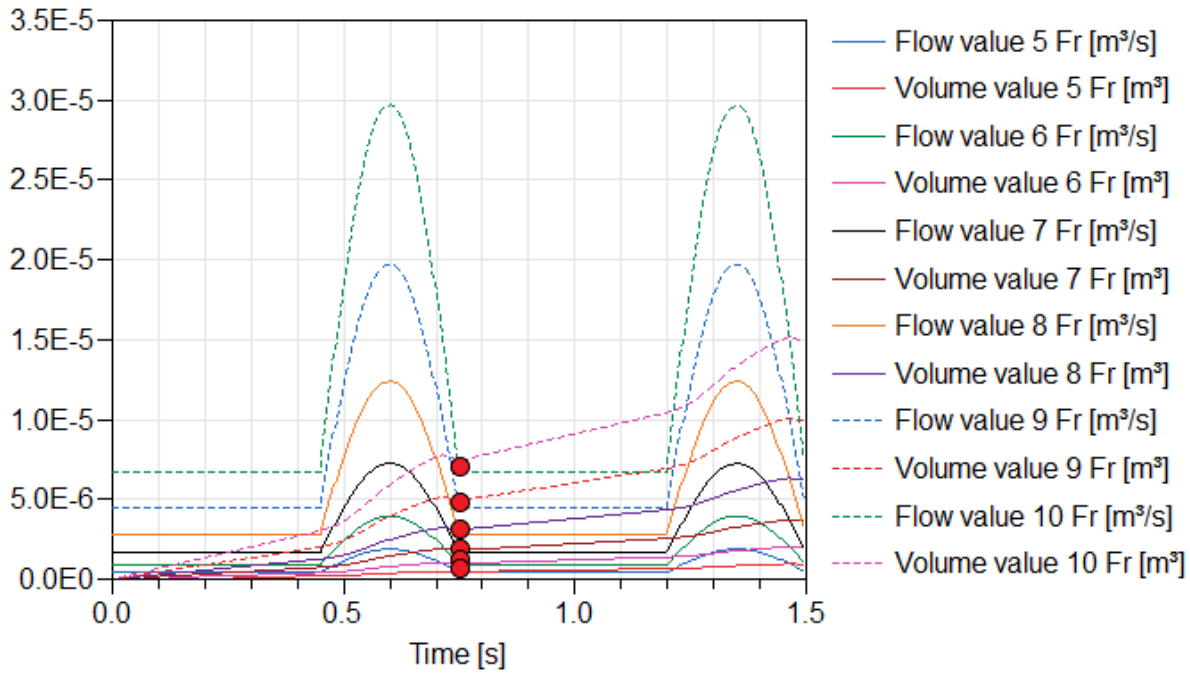
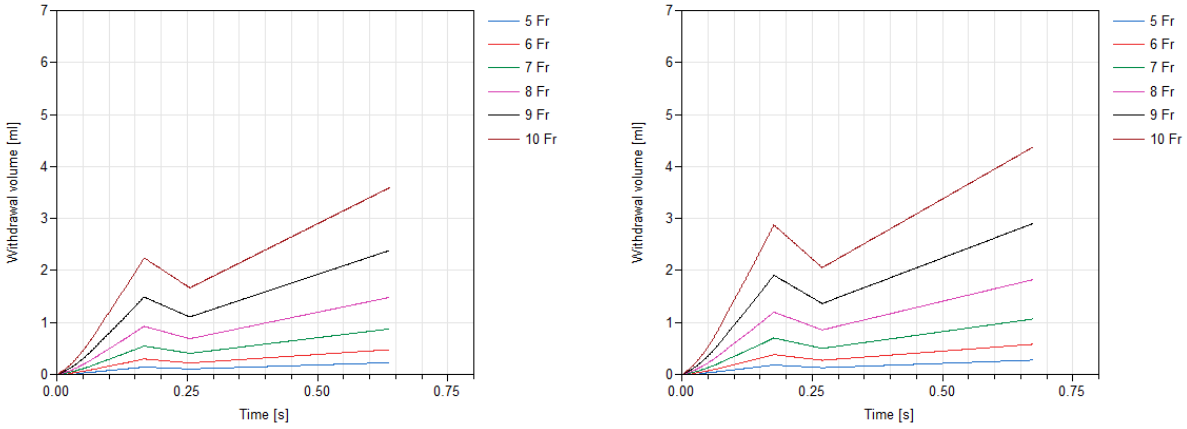


Figure 29: Flow rate profiles throughout the cardiac cycle and the variation with time of the volume value withdrawn from left ventricle by the drainage lumen of the double lumen arterial cannula, EBF 4 L/min. The red circles depict volume values withdrawn from left ventricle for one cardiac cycle

at LV unloading. The conducted study indicates that the size of the drainage lumen is a more influential factor than EBF for LV decompression by DLAC during VA-ECMO therapy. Increasing of EBF value, during the application of a certain size of the drainage lumen, only slightly decreased cardiac loading.

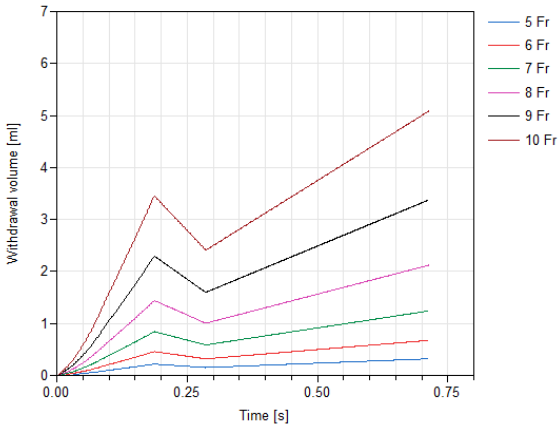
During the simulation, a reverse flow, throughout the drainage lumen was observed (Figure 33); this can be caused by interactions of the pressures in the Y connector, and/or the pressure changes in LV throughout the cardiac cycle. Nevertheless, to establish the cause it is necessary to conduct additional investigations.

From the experiment with large animal models of CS it was determined, that with increases of EBF the LV ESV increased from 64 ml (baseline) to 70 ml, 74 ml, 78 ml and 83 ml, respectively (EBF 1–5 L/min) (Table 2); thereby, ESV is increased by 6 ml, 10 ml,

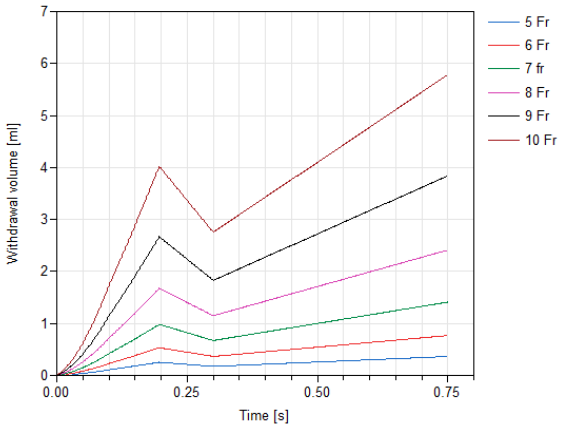


(a) EBF 1 L/min

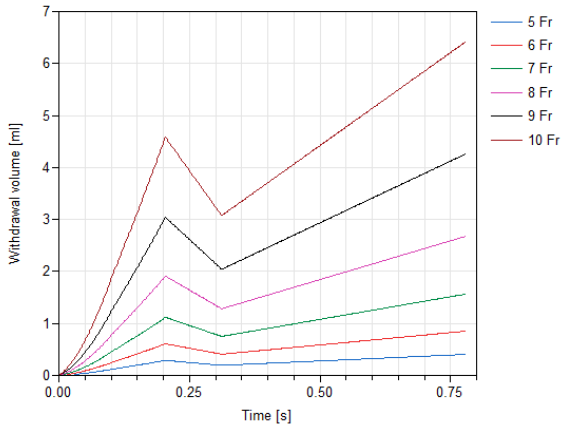
(b) EBF 2 L/min



(c) EBF 3 L/min



(d) EBF 4 L/min



(e) EBF 5 L/min

Figure 30: Withdrawal volume values from left ventricle by various sizes of double lumen arterial cannula drainage lumen in the Modelica interface. The values can be found in Table 3. EBF - extracorporeal blood flow. a) EBF 1 L/min; b) EBF 2 L/min; c) EBF 3 L/min; d) EBF 4 L/min; e) EBF 5 L/min

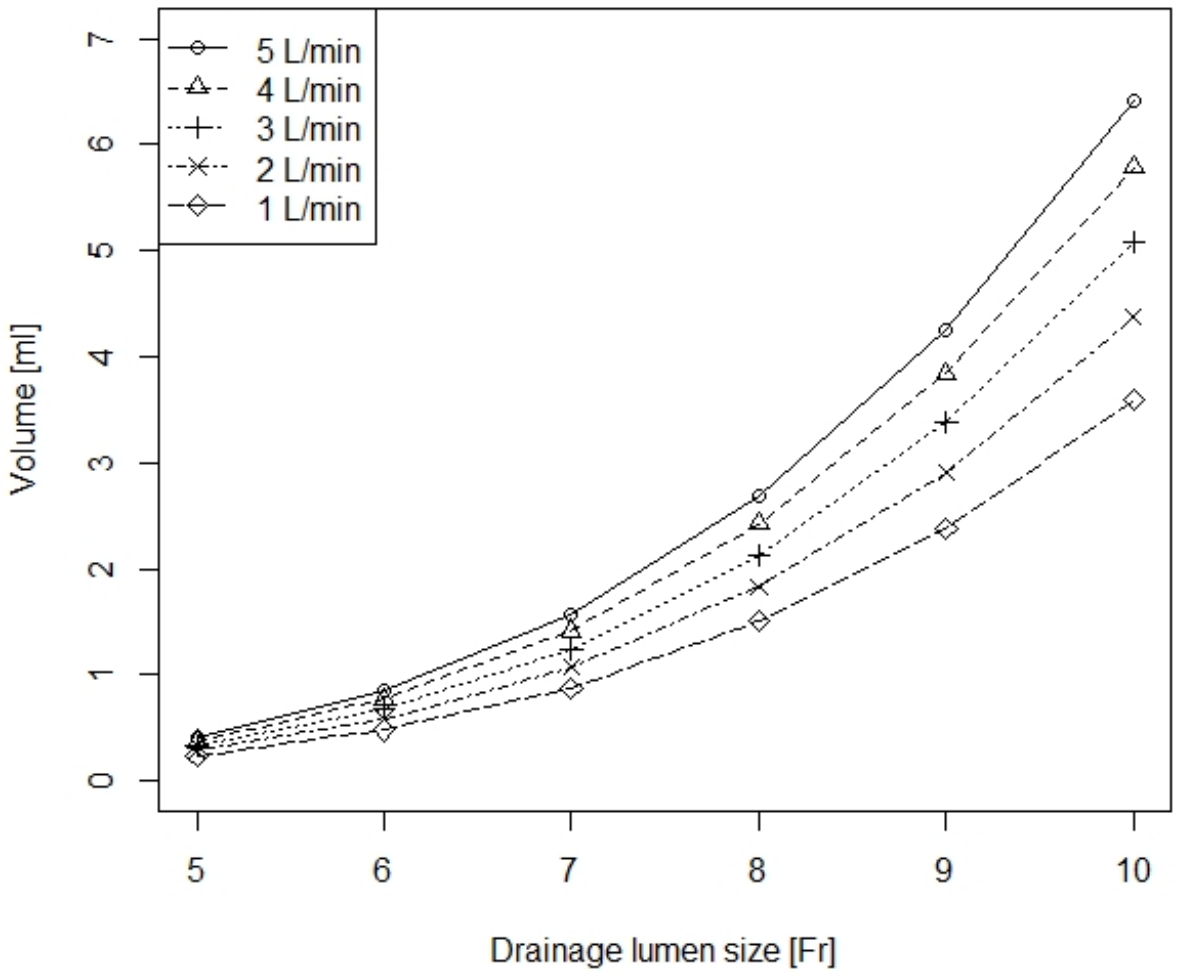


Figure 31: Withdrawal volume values for a cardiac cycle according to the size of drainage lumen of the double lumen arterial cannula. The values can be found in Table 3

14 ml, 19 ml with increasing EBF from 1 L/min to 2 L/min, from 2 L/min to 3 L/min, from 3 L/min to 4 L/min, from 4 L/min to 5 L/min, respectively. Table 3 presents the simulation results of volume values withdrawn from LV for one cardiac cycle. Drainage lumen size range from 5 Fr to 10 Fr, EBF value varies from 1 L/min to 5 L/min. As a result of withdrawal the stagnated blood from LV by the drainage lumen of DLAC, 5 Fr drainage lumen unload LV by 5 %, 3.3 %, 2.7 %, 2 %, during EBF 2 L/min, 3 L/min, 4 L/min, 5 L/min respectively;

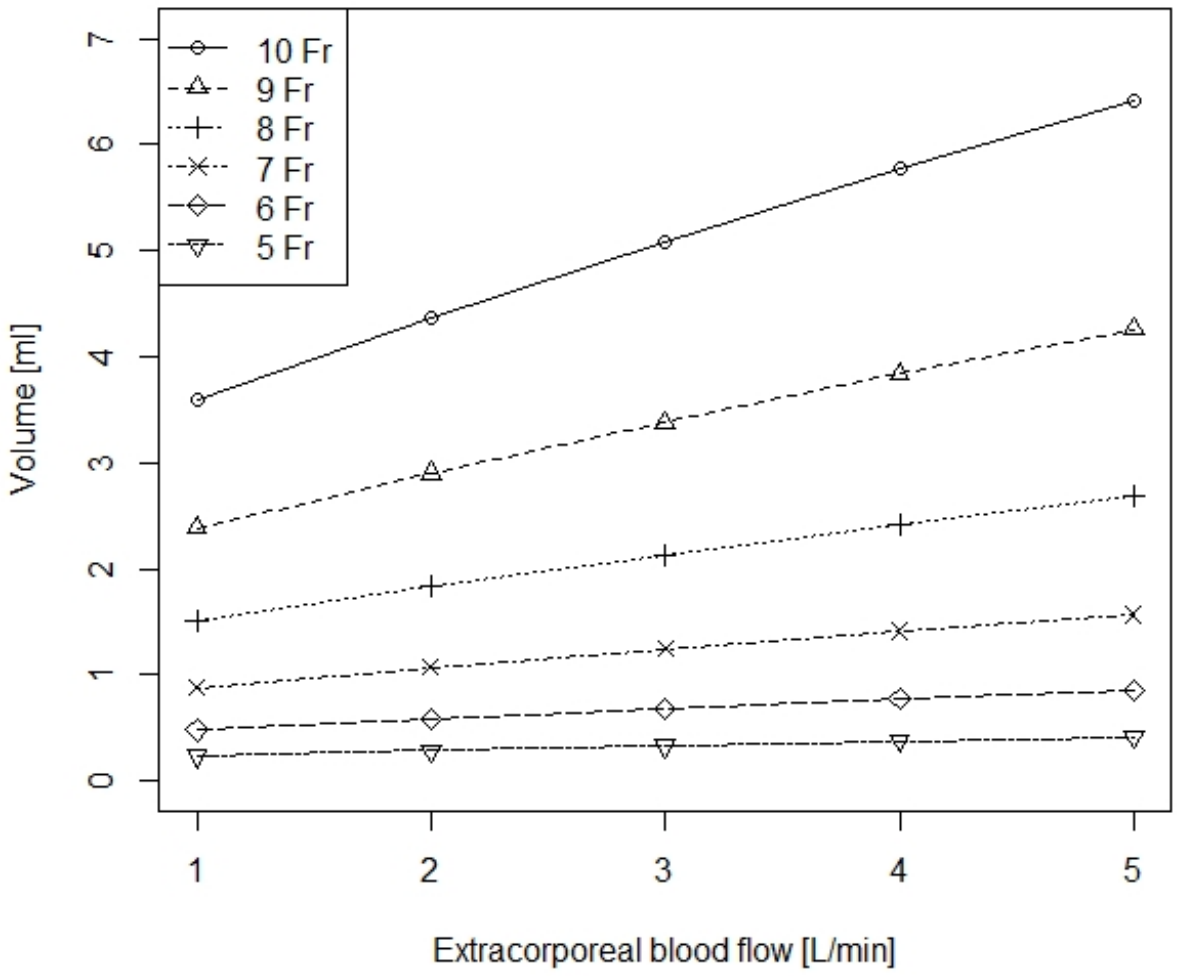


Figure 32: The effect of veno-arterial extracorporeal membrane oxygenation blood flow on withdrawal volume value by the drainage lumen of the double lumen arterial cannula for the cardiac cycle. The values can be found in Table 3

6 Fr drainage lumen withdrew 10%, 7%, 5 %, 4 % of stagnated blood during EBF 2 L/min, 3 L/min, 4 L/min, 5 L/min respectively; 7 Fr drainage lumen withdrew from 18 % to 12 %, 10 %, 8 % during EBF from 1 L/min to 5 L/min; 8 Fr drainage lumen withdrew 31 %, 21 %, 17 %, 14 % of stagnated blood during EBF 2 L/min, 3 L/min, 4 L/min, 5 L/min respectively; 9 Fr drainage lumen withdrew from 48 % to 34 %, 27 %, 22 % during EBF from 1 L/min to

Table 3: Simulated results of blood volume drained from left ventricle for single cardiac cycle by the drainage lumen of the double lumen arterial cannula during veno-arterial extracorporeal membrane oxygenation

Drainage lumen size [Fr]	Extracorporeal blood flow				
	1 L/min	2 L/min	3 L/min	4 L/min	5 L/min
	Withdrawn blood volume during single cardiac cycle [ml]				
5	0.232	0.282	0.328	0.373	0.414
6	0.476	0.580	0.675	0.768	0.852
7	0.876	1.067	1.241	1.411	1.565
8	1.504	1.833	2.131	2.423	2.688
9	2.384	2.905	3.377	3.840	4.260
10	3.591	4.375	5.087	5.784	6.417

5 L/min respectively; 10 Fr drainage lumen unloaded LV by 73 %, 51 %, 41 %, 34 %, during EBF 2 L/min, 3 L/min, 4 L/min, 5 L/min respectively (Figure 34) compared with baseline. The percentages of LV unloading were calculated using the results of simulations.

It is absolutely understandable that the larger the size of the DLAC drainage lumen that is be used, the greater the degree of unloading that will be achieved. However, human physiological features must be taken into account; the DLAC cannot exceed a limited size which is defined by the physiological properties of human blood vessels. In addition, DLAC must have the appropriate size of reinfusion lumen in order to provide the necessary flow. To ensure sufficient tissue oxygenation, an appropriate flow through the reinfusion lumen is required. The cross-sectional area of the DLAC reinfusion lumen approximately corresponds to the 15 Fr cannula; DLAC cross-sectional area equals 20.67 mm^2 (Figure 35).

An increasing of one lumen increased the whole size of the cannula; the common size of the femoral artery in an adult is 6.6 mm in diameter (3.9 – 8.9 mm) [108], and the size of the DLAC cannot exceed these dimensions. DLAC with a 10 Fr drainage lumen has diameter

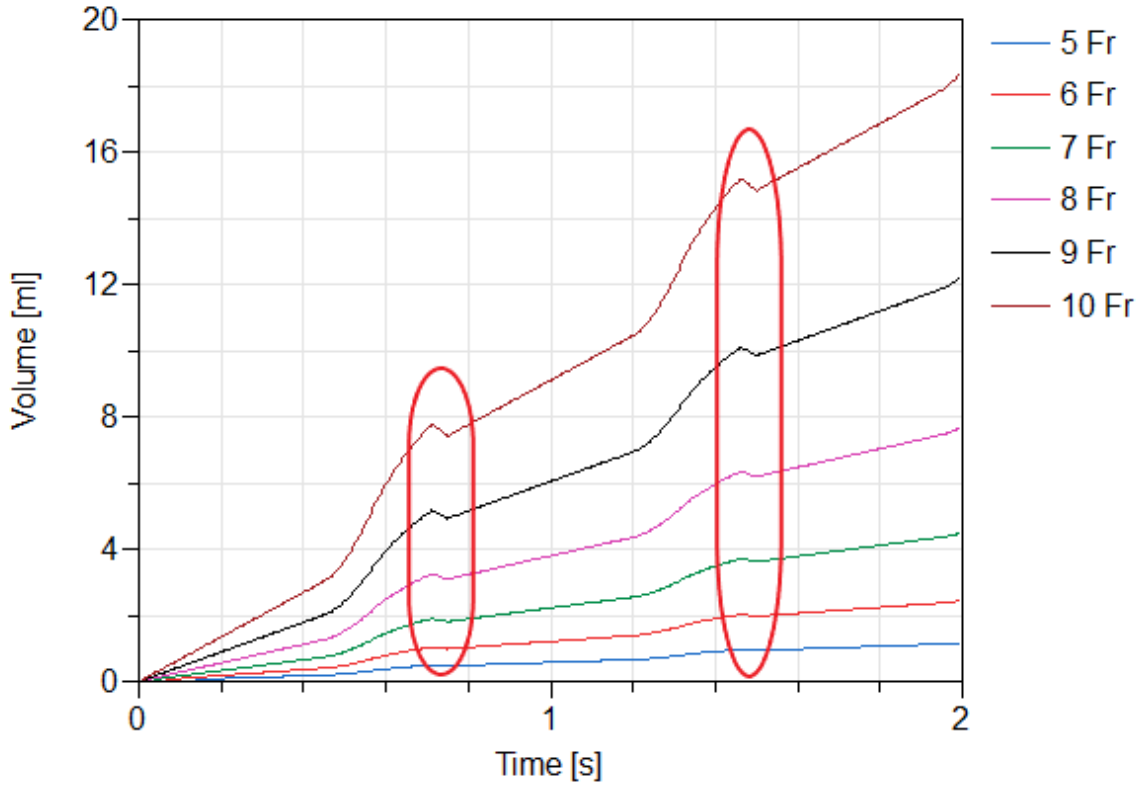


Figure 33: Reverse flow throughout the drainage lumen during left ventricular unloading by double lumen arterial cannula, extracorporeal blood flow 4 L/min

7 mm; this size is appropriate for insertion to the common femoral artery of an adult person. In addition, the smaller the size of the cannula, the lower the probability of side effects such as bleeding, the risk of vascular damage, ischemia, and obstruction of arteries.

The results of conducted simulations have estimated that the DLAC for VA-ECMO with a 10 Fr drainage lumen presents a promising solution to achieve reduction of the LV loading during VA-ECMO, and it could be considered a less invasive than by the methods proposed to date. The smaller diameter of drainage lumen could be used; nevertheless, a lesser degree of LV unloading could be achieved.

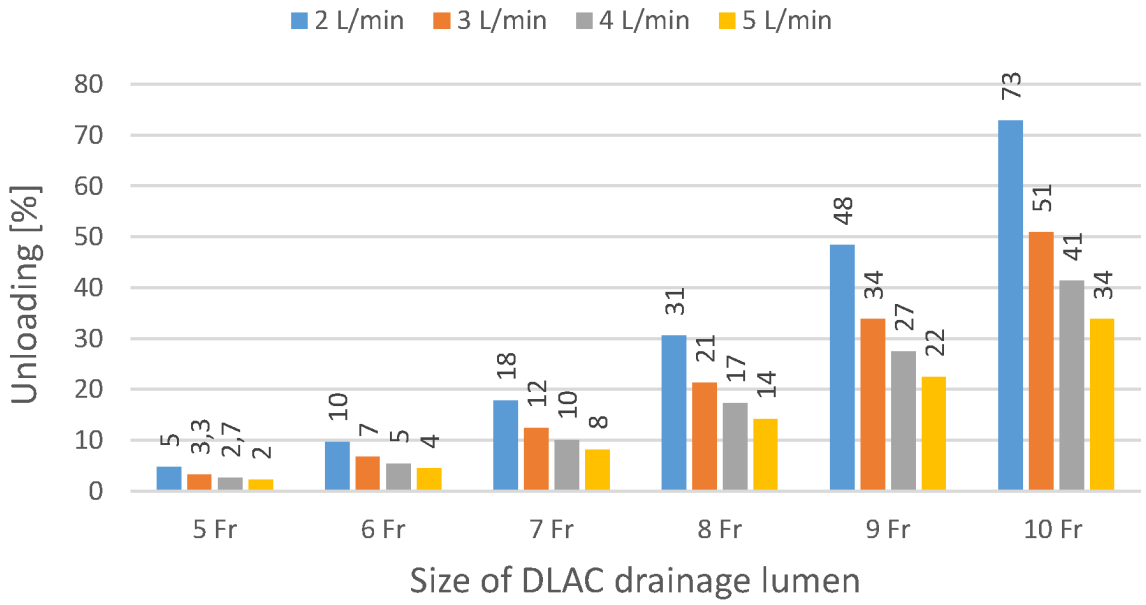


Figure 34: The percentage of left ventricular unloading during veno-arterial extracorporeal membrane oxygenation by double lumen arterial cannula

5.3.2 Impact of venous cannula size on DLAC unloading capacities

The results of the simulation indicate that with decreasing of the size of the venous cannula from 29 Fr to 18 Fr, an increase in blood withdrawal by the DLAC drainage lumen from LV was observed from 0.258 ml to 0.31 ml during EBF 2 L/min, from 0.29 ml to 0.373 ml during EBF 3 L/min, from 0.32 ml to 0.436 ml during EBF 4 L/min, from 0.345 ml to 0.496 ml, during EBF 5 L/min throughout 5 Fr drainage lumen; from 0.532 ml to 0.637 ml, from 0.597 ml to 0.766 ml, from 0.659 ml to 0.895 ml, from 0.71 ml to 1.017 ml during EBF 2 L/min, 3 L/min, 4L/min, 5L/min respectively throughout 6 Fr drainage lumen; from 0.98 ml to 1.168 ml, from 1.1 ml to 1.404 ml, from 1.213 ml to 1.641 ml, from 1.307 ml to 1.866 ml, during EBF 2 L/min, 3 L/min, 4L/min, 5L/min respectively throughout 7 Fr drainage lumen; from 1.688 ml to 2 ml, from 1.895 ml to 2.404 ml, from 2.089 ml to 2.81 ml, from 2.251 ml to 3.194 ml, during EBF 2 L/min, 3 L/min, 4 L/min, 5 L/min respectively

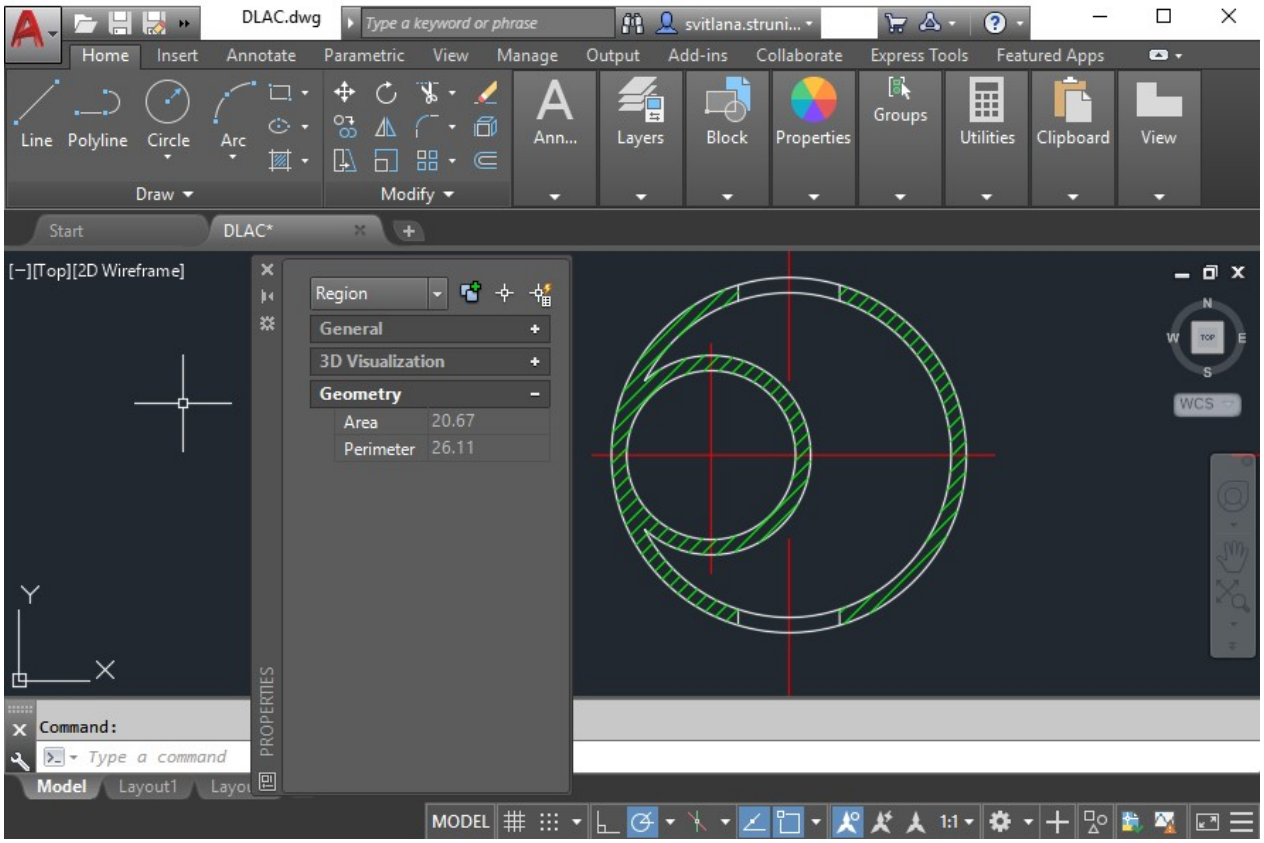


Figure 35: The cross-sectional area of the double lumen arterial cannula reinfusion lumen

throughout 8 Fr drainage lumen; from 2.686 ml to 3.155 ml, from 3.016 ml to 3.791 ml, from 3.325 ml to 4.432 ml, from 3.583 ml to 5.038 ml, during EBF 2 L/min, 3 L/min, 4 L/min, 5 L/min respectively throughout 9 Fr drainage lumen; from 4.069 ml to 4.722 ml, from 4.569 ml to 5.674 ml, from 5.036 ml to 6.632 ml, from 5.427 ml to 7.539 ml during EBF 2 L/min, 3 L/min, 4 L/min, 5 L/min respectively throughout 10 Fr drainage lumen. The results of simulation with venous cannula sizes from 18 Fr to 29 Fr and for DLAC drainage lumen sizes from 5 Fr to 9 Fr are presented in Appendix F.

The Figure 36 depicts withdrawal volume values for a cardiac cycle by 10 Fr drainage lumen of DLAC, with venous cannulas from 18 Fr to 29 Fr, during various EBF in the Modelica interface. The Figure 37 presents withdrawal volume values by 10 Fr drainage lumen, with venous cannula sizes from 18 Fr to 29 Fr for one cardiac cycle; EBF value varies from 1 L/min to 5 L/min.

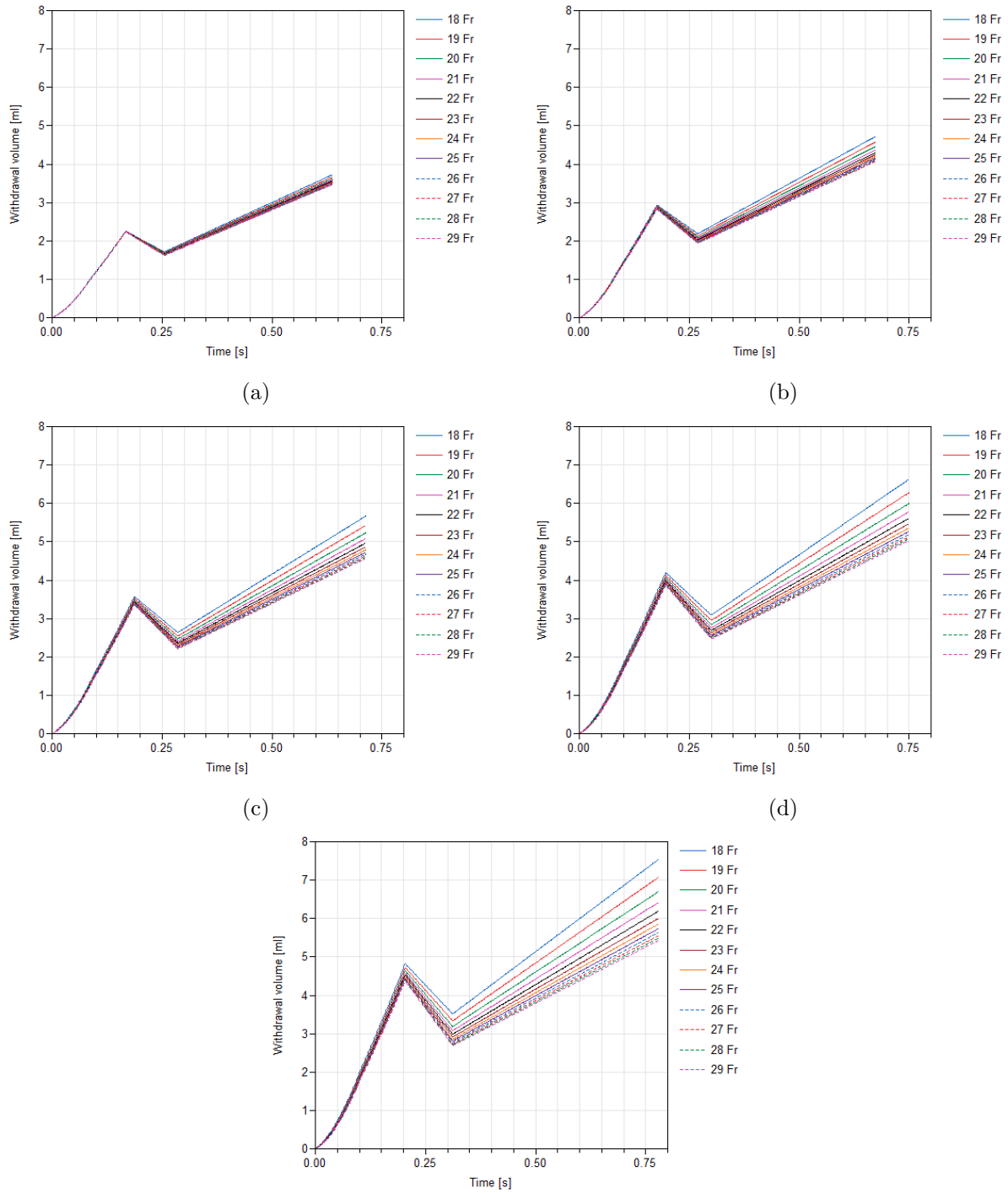


Figure 36: Withdrawal volume values for a cardiac cycle by 10 Fr drainage lumen, with venous cannulas from 18 Fr to 29 Fr in the Modelica interface. EBF - extracorporeal blood flow. a) EBF 1 L/min; b) EBF 2 L/min; c) EBF 3 L/min; d) EBF 4 L/min; e) EBF 5 L/min

The Table 4 presents the simulation results of volume values withdrawn from LV for one cardiac cycle by 10 Fr drainage lumen of DLAC. EBF value varies from 1 L/min to 5 L/min. The venous cannula size varies from 18 Fr to 29 Fr.

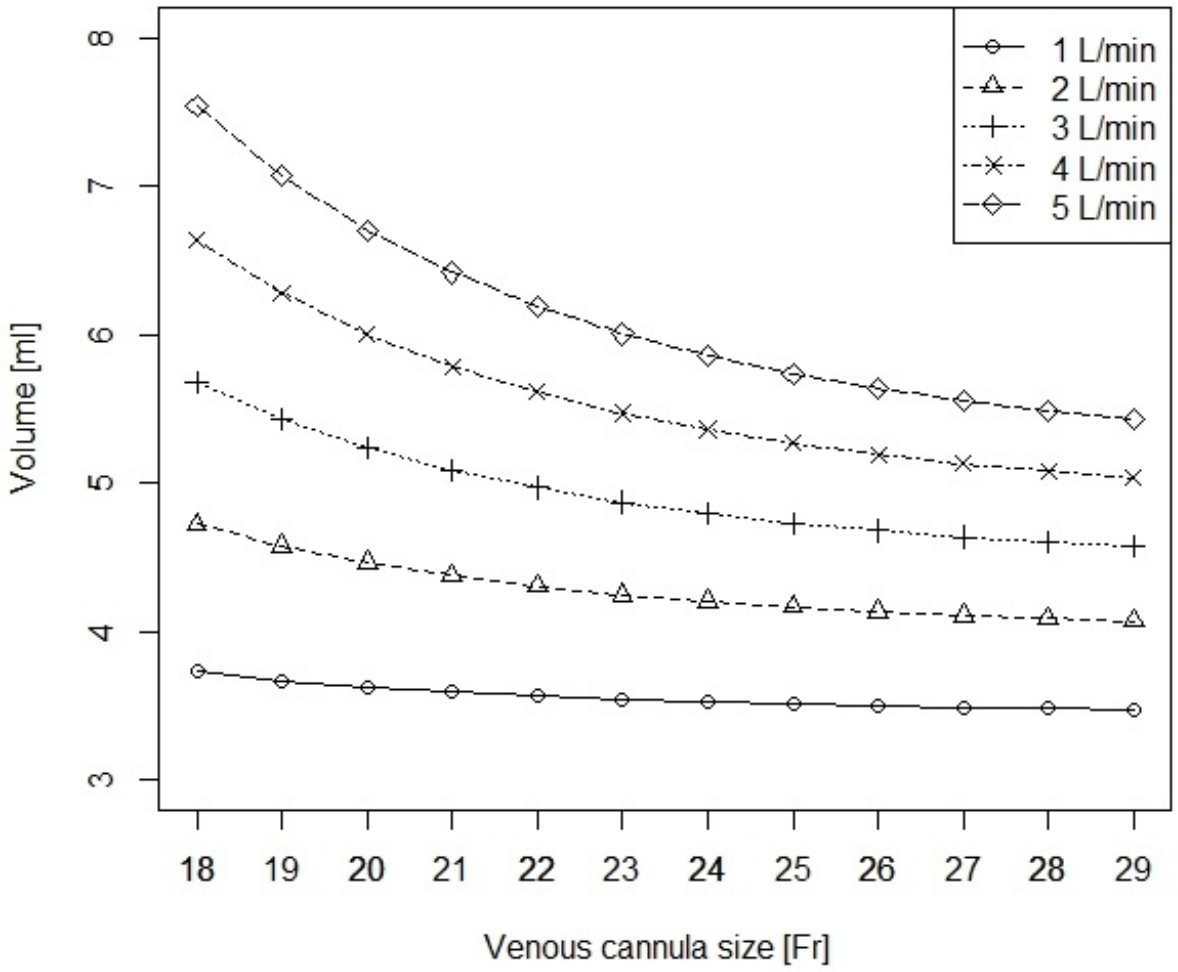


Figure 37: Blood volume withdrawn from left ventricle by 10 Fr drainage lumen of the double lumen arterial cannula for a cardiac cycle with venous cannula sizes from 18 Fr to 29 Fr. The values can be found in Table 4

As was mentioned above, VA-ECMO, and increasing EBF causes increasing ESV, witch means stagnation of the blood in the LV. The drainage lumen of DLAC withdraws the stag-

nated blood from LV, and as a result LV overload might be reduced. The percentages of LV unloading were calculated using the results of simulations on the created model. With a decrease of ECMO venous cannula size, LV unloading seems to have been increased in comparison with baseline. The data for the unloading percentages are presented in Appendix H.

Table 4: Simulated results of blood volume drained from left ventricle by 10 Fr drainage lumen of double lumen arterial cannula, with venous cannula sizes from 18 Fr to 29 Fr

ECMO venous cannula size [Fr]	Extracorporeal blood flow				
	1 L/min	2 L/min	3 L/min	4 L/min	5 L/min
	Withdrawn blood volume during single cardiac cycle [ml]				
18	3.726	4.722	5.674	6.632	7.539
19	3.670	4.578	5.431	6.281	7.074
20	3.625	4.463	5.236	5.999	6.701
21	3.591	4.375	5.087	5.784	6.417
22	3.563	4.305	4.968	5.613	6.190
23	3.541	4.247	4.870	5.471	6.003
24	3.523	4.202	4.794	5.360	5.856
25	3.509	4.165	4.731	5.270	5.737
26	3.497	4.133	4.678	5.193	5.635
27	3.487	4.108	4.635	5.132	5.554
28	3.479	4.087	4.600	5.080	5.486
29	3.472	4.069	4.569	5.036	5.427

Figure 38 depicts the percentage of LV unloading during VA-ECMO by 10 Fr drainage lumen of DLAC with ECMO venous cannula from 18 Fr to 21 Fr, during various EBF.

As was mentioned in the previous paragraph, the larger the size of the DLAC drainage lumen that is used, the greater the degree of unloading that will be achieved. Nevertheless, the size of the DLAC drainage lumen must not exceed 10 Fr on account of human physiological

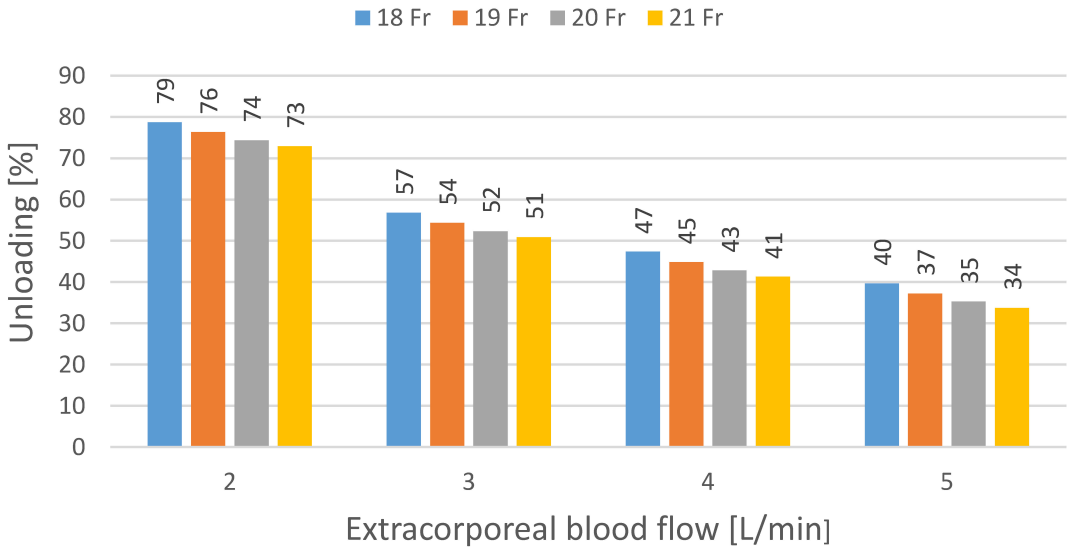


Figure 38: Percentage of left ventricular unloading during veno-arterial extracorporeal membrane oxygenation by 10 Fr double lumen arterial cannula drainage lumen with venous cannula sizes from 18 Fr to 21 Fr

features. This paragraph describes the circumstances of a possible increase in the degree of LV unloading by increasing flow through the drainage lumen of DLAC, without an increase in DLAC size. In this paragraph, the comparison of the degree of LV unloading with the application of venous cannulas from 18 Fr to 29 Fr is done. The reason for choosing venous cannula sizes from 18 Fr to 29 Fr is that standard ECMO venous cannula sizes for adults are from 18 Fr to 29 Fr. The venous cannula 21 Fr was used in the study mentioned in the paragraph above.

The simulation study indicates, that with decreasing venous cannula size, the percentage of LV loading during VA-ECMO decreases. The flow through the drainage lumen of DLAC is increased with decreasing venous cannula size; therefore, achieving a better result of LV unloading during VA-ECMO. Consequently, the smaller the venous cannula that is used, the higher the value of LV unloading that is achieved by the drainage lumen of DLAC; in addition, as was mentioned before, the lower the size of the cannula, the lower the probability of the occurrence of complications associated with the introduction of peripheral cannulas.

5.4 The pilot study with double lumen arterial cannula in porcine model of cardiogenic shock

The aim of the experiment was to research and establish the impact of DLAC aplication during the VA-ECMO therapy on the LV performance parameters in a porcine model of a CS. The animal underwent VA-ECMO implantation under general anesthesia and artificial ventilation. After inducing of acute CS with signs of tissue hypoxia, hemodynamic and cardiac performance parameters were measured with a clamped drainage lumen of DLAC and consistently unclamped drainage lumen of DLAC. DLAC with a clamped drainage lumen acts as a standard peripheral cannula; therefore, the collected data during clamped drainage lumen were presented as hemodynamic and cardiac performance parameters using standard peripheral cannula. For the measurement of hemodynamic and cardiac performance parameters a pressure-volume loop catheter (placed in the LV), arterial and venous catheters, and pulmonary artery catheter were used.

With the application of DLAC instead of standard arterial cannula during VA-ECMO, an decreasing in ArtD was observed from 99.0±5.0 mmHg to 66.67±6.6 mmHg ($P<0.05$) (Figure 39a); SBP decreased from 127.2±7.4 mmHg to 97.17±8.4 mmHg ($P<0.05$) (Figure 39b); EDP decreased from 21.83±0.9 mmHg to 16±0.51 mmHg ($P<0.05$) (Figure 39c); ESV decreased from 127.8±2.5 ml to 113.8±3.6 ml ($P<0.05$) (Figure 39d), LVEF (increased 25.5±1.4 % to 32.67±2.2 %; $P<0.05$) (Figure 39e). There was no significant difference in EDV (decreased 171.5±1.9 ml to 168±3 ml; $P=0.2$) (Table 5), SV (increased from 43.67±2.6 ml to 54.83±4.33 ml; $P=0.051$) (Table 5), and dP/dt (increased from 721.2±85.2 mmHg/s to 907.8±92.5 mmHg/s; $P=0.16$) (Table 5).

Table 5 presents selected hemodynamic parameters of the animal model of CS during VA-ECMO with the use of standard arterial cannula and using DLAC during VA-ECMO.

As a consequence of applying VA-ECMO, as a side effect, the overload and impairment of LV function might occur. The findings from this study provide evidence that the use of DLAC

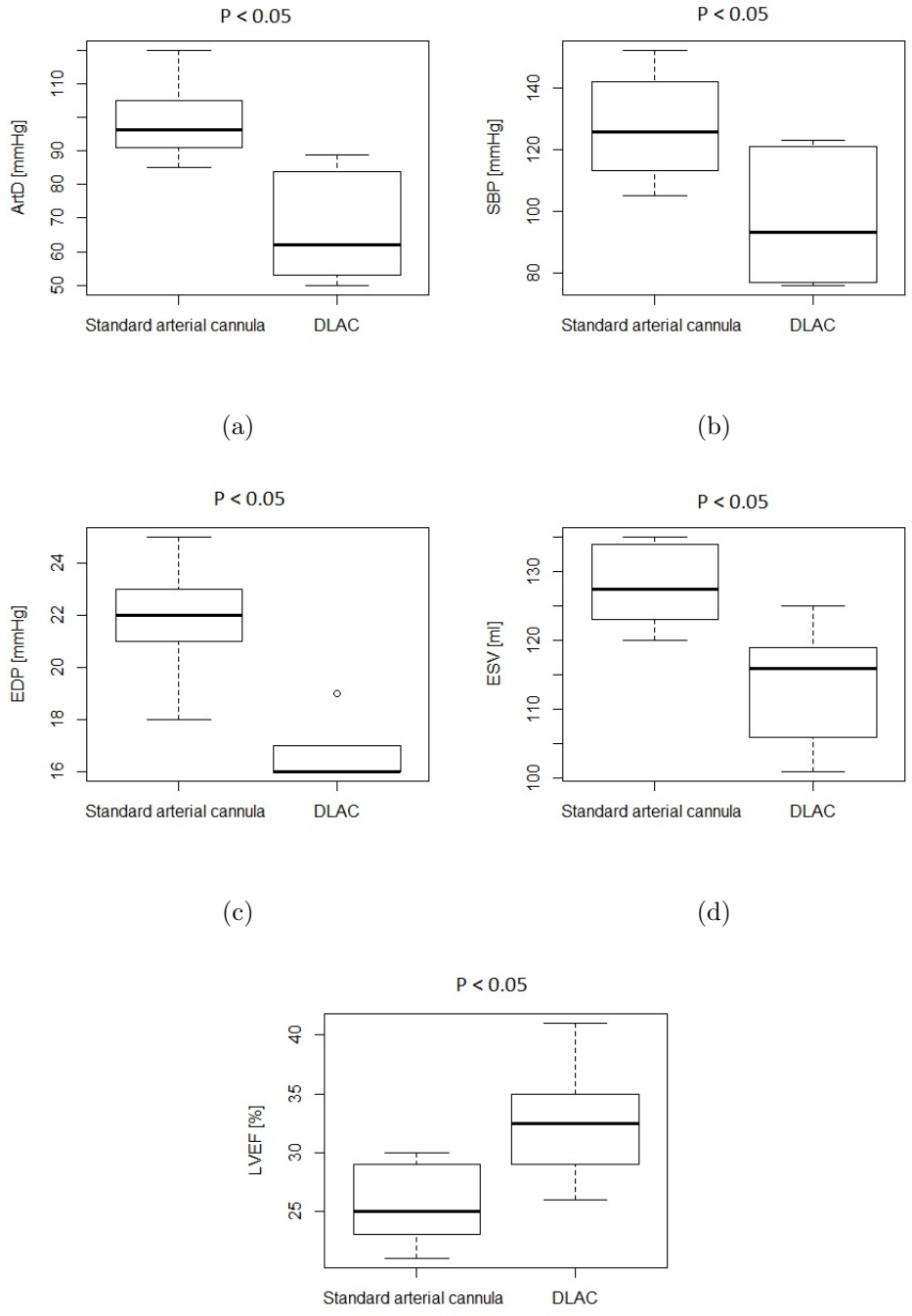


Figure 39: The effect of using double lumen arterial cannula during veno-arterial extracorporeal membrane oxygenation on left ventricular functional parameters in a porcine model of cardiogenic shock. ArtD - arterial diastolic pressure, SBP - systolic blood pressure, EDP - end-diastolic pressure, ESV - end-systolic volume, LVEF - ejection fraction

Table 5: The selected hemodynamic parameters in a porcine model of cardiogenic shock during veno-arterial extracorporeal membrane oxygenation with using standard arterial cannula and with the use of DLAC during VA-ECMO. The values are reported as mean ± the standard error of the mean

Parameters	Standard arterial cannula	DLAC	P value
Left ventricular end-diastolic volume [ml]	171.5±1.9	168±3	0.13
Left ventricular stroke volume [ml]	43.67±2.6	54.83±4.33	0.051
Left ventricular contractility [mmHg/s]	721.2±85.2	907.8±92.5	0.16

instead of a standard peripheral cannula during VA-ECMO had a beneficial effect on selected LV parameters. The application of DLAC in medical practice can make the elimiantion of LV loading possible, or at least to achieve a LV loading reduction to prevent LV overload during VA-ECMO therapy. Using DLAC might be an alternative method, which could be considered less-invasive than currently used methods for LV unloading during VA-ECMO. The analysis of archived data indicate that ArtS, ArtD, SBP, EDP, ESV were significantly lover ($P<0.05$) and LVEF was significantly greater ($P<0.05$) during VA-ECMO with DLAC than that during VA-ECMO with a standard arterial cannula.

One of the most important aspects of VA-ECMO is the impairment of performance of the LV [73] during ECMO therapy. Numerous studies have indicated that direct LV decompression by placing a vent into the LV eliminate LV function deterioration, organ function deterioration, and improve survival outcomes [27, 29, 120]. According to the obtained information, Impella is considered the most powerful tool for LV decompression during VA-ECMO [89, 8]; nonetheless the application of Impella may lead to significant hemolysis [12]. Barbone et al. [13], and Hong et al. [42] report trans-aortic catheter venting of LV during ECMO (the vent was connected to the venous site of the ECMO circuit) which leads to acceptable LV unloading. These studies correspond with the conducted study with DLAC

in a porcine model of CS. In addition, using DLAC do not require the additional interventions and could be considered a less-invasive method of LV unloading, than other methods proposed to this date.

The limitations of the experiment related to small numbers. To better understand the impact of DLAC on LV performance more accurate population-based data sets that contain accurate clinical information are needed. A higher powered study is necessary to verify and confirm DLAC effects on LV performance. In future studies, it will be important to investigate the impact of using DLAC on outcomes such as time to recovery, medical complications, and cost.

6 Summary and future perspectives

The outcomes of VA-ECMO is improved with the appearance of newer technologies, and the role of ECMO in the treatment of patients with severe CS and CA refractory to conventional medical therapy and standard resuscitation methods has continued to evolve.

Biomedical engineering is a broad field that covers a wide range of activities.

"Bioengineering is usually defined as a basic research-oriented activity closely related to biotechnology and genetic engineering ... on the other hand, apply electrical, mechanical, chemical, optical, and other engineering principles to understand, modify, or control biologic (i.e., human and animal) systems, as well as design and manufacture products that can monitor physiologic functions and assist in the diagnosis and treatment of patients" [19].

Among other things, biomedical engineering involves advising manufacturers of medical devices on promising improvements based on clinical experience; the application and implementation of medical technologies to optimize the delivery of medical care. These aspects of biomedical engineering are realized in this thesis. The thesis presents, an alternative method of LV unloading, which has the potential for reducing the invasiveness of LV unloading during VA-ECMO therapy. The incorporation of the developed method of LV unloading in medical practice is going to improve the emptying of the LV during ECMO, and to prevent LV overload during VA-ECMO therapy. It is intended that the findings will contribute to the mitigation of such ECMO complications as LV overload; furthermore, elimination of the complications, of currently existing methods for LV decompression, such as an additional source of bleeding, infection, and longer recovery time of ECMO treated patients.

In the thesis were described in detail, hemodynamic and cardiac performance parameters in ECMO treated individuals with CA and CS. Then currently existing methods were described for LV unloading in VA-ECMO treated individuals. Furthermore, the impact of ECMO therapy on LV performance in large animal models of CS was investigated. The experimental data demonstrated unsatisfactory LV unloading during high-flow VA-ECMO; it may

cause impairment of LV performance in a flow-dependent manner in CS. ECMO can induce LV dilatation, pulmonary edema, and deterioration of LV function. The adequate drainage of LV during VA-ECMO is a crucial factor in the patient outcome. The existing methods for LV unloading require additional interventions [110], which increase the risk of complications such as infection, bleeding and longer recovery times. In the thesis an alternative method, which has the potential for reducing the invasiveness of LV unloading during VA-ECMO therapy is proposed. The application of the DLAC might be considered less-invasive approach than currently existing methods for reducing LV overload during VA-ECMO; the DLAC might unload the LV and infused oxygenated blood to the circulation while requiring only one puncture. The DLAC is a patented invention; it is a one piece reinforced cannula with side holes at the tips of the lumens. This configuration avoids kinking or collapse of the cannula, decreases hemolysis, and allows a higher flow rate and greater reduction of shear rate. Based on acquired data from large animal models of CS, the model was created, and the value of LV decompression by using the proposed alternative method of LV unloading was established. The sufficient size of drainage lumen of DLAC was identified. The simulation study demonstrates that the value of withdrawal volume by the drainage lumen, connected to the venous site of the ECMO circuit, depends mainly on the size of the drainage lumen. The study indicates that DLAC with 10 Fr drainage lumen achieves the purpose of reducing LV loading, and meets the typical physiological dimensions of the femoral artery of an adult. Based on the modeling and simulation, circumstances under which to increase the value of LV decompression by using DLAC without increasing DLAC size were identified. The method of increasing flow through the drainage lumen of DLAC, and thus to provide a greater degree of LV unloading is decreasing ECMO venous cannula. The simulated study indicates that the optimal conditions for achieving the best result of LV unloading by DLAC during ECMO are as large as possible drainage lumen and as small as possible ECMO venous cannula. The pilot study was conducted to investigate the impact of the DLAC during VA-ECMO on LV performance in large animal model of CS. The pilot experiment indicated significant

improvement in selected hemodynamic parameters and LV performance.

DLAC presents a promising solution and has the potential for reducing the invasiveness of LV unloading during VA-ECMO therapy. The application of the DLAC might be a novel method of LV overload reduction, which gives good grounds for expecting to mitigate negative sequelae of VA-ECMO; it is intended that the implication of DLAC in medical practice will contribute to the mitigation of ECMO complications such as LV overload.

References

[1] Select 3d® & EOPA 3d® arterial cannulae - medtronic - PDF catalogs — technical documentation. http://pdf.medicalexpo.com/pdf/medtronic/select-3d-eopa-3d-arterial-cannulae/70691-134576.html. Accessed: 2019-1-6.

[2] Bioinspired coating for medical devices repels blood and bacteria. https://wyss.harvard.edu/bioinspired-coating-for-medical-devices-repels-blood-and-bacteria/, Oct. 2014. Accessed: 2019-1-6.

[3] Abdel-Sayed, S., Favre, J., and von Segesser, L. K. How to prevent venous cannula orifice obstruction during extracorporeal circulation. *Perfusion 30*, 3 (Apr. 2015), 187–194.

[4] Abrams, D. C., Brodie, D., Rosenzweig, E. B., Burkart, K. M., Agerstrand, C. L., and Bacchetta, M. D. Upper-body extracorporeal membrane oxygenation as a strategy in decompensated pulmonary arterial hypertension. *Pulm. Circ. 3*, 2 (Apr. 2013), 432–435.

[5] Acheampong, B., Johnson, J. N., Stulak, J. M., Dearani, J. A., Kushwaha, S. S., Daly, R. C., Haile, D. T., and Schears, G. J. Postcardiotomy ecmo support after high-risk operations in adult congenital heart disease. *Congenital heart disease 11*, 6 (2016), 751–755.

[6] Aissaoui, N., Guerot, E., Combes, A., Delouche, A., Chastre, J., Leprince, P., Leger, P., Diehl, J. L., Fagon, J. Y., and Diebold, B. Two-dimensional strain rate and doppler tissue myocardial velocities: analysis by echocardiography of hemodynamic and functional changes of the failed left ventricle during different degrees of extracorporeal life support. *J. Am. Soc. Echocardiogr. 25*, 6 (June 2012), 632–640.

[7] Aiyagari, R. M., Rocchini, A. P., Remenapp, R. T., and Graziano, J. N. Decompression of the left atrium during extracorporeal membrane oxygenation using a transseptal cannula incorporated into the circuit. *Crit. Care Med. 34*, 10 (Oct. 2006), 2603–2606.

[8] Amarelli, C., Musumeci, F., Loforte, A., Montalto, A., Di Franco, S., and Hernandez-Montfort, J. Flow optimization, management, and prevention of lv distention during va-ecmo. In *Advances in Extra-corporeal Perfusion Therapies*. IntechOpen, 2018.

[9] Anastasiadis, K., Chalvatzoulis, O., Antonitsis, P., Tossios, P., and Papakonstantinou, C. Left ventricular decompression during peripheral extracorporeal membrane oxygenation support with the use of the novel ivac pulsatile paracorporeal assist device. *The Annals of thoracic surgery 92*, 6 (2011), 2257–2259.

[10] Arlt, M., Philipp, A., Voelkel, S., Schopka, S., Husser, O., Hengstenberg, C., Schmid, C., and Hilker, M. Early experiences with miniaturized extracorporeal life-support in the catheterization laboratory. *Eur. J. Cardiothorac. Surg. 42*, 5 (Nov. 2012), 858–863.

[11] Avalli, L., Maggioni, E., Sangalli, F., Favini, G., Formica, F., and Fumagalli, R. Percutaneous left-heart decompression during extracorporeal membrane oxygenation: an alternative to surgical and transeptal venting in adult patients. *ASAIO J. 57*, 1 (Jan. 2011), 38–40.

[12] Badiye, A. P., Hernandez, G. A., Novoa, I., and Chaparro, S. V. Incidence of hemolysis in patients with cardiogenic shock treated with impella percutaneous left ventricular assist device. *Asaio Journal 62*, 1 (2016), 11–14.

[13] Barbone, A., Malvindi, P. G., Ferrara, P., and Tarelli, G. Left ventricle unloading by percutaneous pigtail during extracorporeal membrane oxygenation. *Interactive cardiovascular and thoracic surgery 13*, 3 (2011), 293–295.

[14] Beckmann, A., Benk, C., Beyersdorf, F., Haimerl, G., Merkle, F., Mestres, C., Pepper, J., Wahba, A., and ECLS Working Group. Position article for the use of extracorporeal life support in adult patients. *Eur. J. Cardiothorac. Surg. 40*, 3 (Sept. 2011), 676–680.

[15] Berdajs, D., Ferrari, E., Michalis, A., Burki, M., Pieterse, C. W., Horrisberger, J., and von Segesser, L. K. New prototype of femoral arterial SmartCannula with anterograde and retrograde flow. *Perfusion 26*, 4 (July 2011), 271–275.

[16] Berdjis, F., Takahashi, M., and Lewis, A. B. Left ventricular performance in neonates on extracorporeal membrane oxygenation. *Pediatric cardiology 13*, 3 (1992), 141–145.

[17] Bonacchi, M., Harmelin, G., Peris, A., and Sani, G. A novel strategy to improve systemic oxygenation in venovenous extracorporeal membrane oxygenation: the "χ-configuration". *J. Thorac. Cardiovasc. Surg. 142*, 5 (Nov. 2011), 1197–1204.

[18] Brehm, C., Schubert, S., Carney, E., Ghodsizad, A., Koerner, M., McCoach, R., and El-Banayosy, A. Left anterior descending coronary artery blood flow and left ventricular unloading during extracorporeal membrane oxygenation support in a swine model of acute cardiogenic shock. *Artificial organs 39*, 2 (2015), 171–176.

[19] Bronzino, J. D., and Peterson, D. R. *Biomedical engineering fundamentals*. CRC press, 2014.

[20] Broomé, M., and Donker, D. W. Individualized real-time clinical decision support to monitor cardiac loading during venoarterial ecmo. *Journal of translational medicine 14*, 1 (2016), 4.

[21] Brunner, M.-E., Banfi, C., and Giraud, R. Venoarterial extracorporeal membrane oxygenation in refractory cardiogenic shock and cardiac arrest. In *Extracorporeal Membrane Oxygenation: Advances in Therapy*, M. S. Firstenberg, Ed. InTech, Sept. 2016.

[22] Condemi, F., Wang, D., Fragomeni, G., Yang, F., Zhao, G., Jones, C., Ballard-Croft, C., and Zwischenberger, J. B. Percutaneous double lumen cannula for right ventricle assist device system: A computational fluid dynamics study. *Biocybern Biomed Eng 36*, 3 (Apr. 2016), 482–490.

[23] Doll, N., Kiaii, B., Borger, M., Bucerius, J., Krämer, K., Schmitt, D. V., Walther, T., and Mohr, F. W. Five-year results of 219 consecutive patients treated with extracorporeal membrane oxygenation for refractory postoperative cardiogenic shock. *Ann. Thorac. Surg. 77*, 1 (Jan. 2004), 151–7; discussion 157.

[24] Donker, D. W., Brodie, D., Henriques, J. P., and Broomé, M. Left ventricular unloading during veno-arterial ecmo: a review of percutaneous and surgical unloading interventions. *Perfusion* (2018), 0267659118794112.

[25] Douflé, G., Roscoe, A., Billia, F., and Fan, E. Echocardiography for adult patients supported with extracorporeal membrane oxygenation. *Critical Care 19*, 1 (2015), 326.

[26] Elmqvist, H., Boudaud, F., Broenink, J., Brück, D., Ernst, T., Fritzson, P., Jeandel, A., Juslin, K., Klose, M., Mattsson, S., et al. Modelicatm-a unified object-oriented language for physical systems modeling. *Tutorial and Rationale, versión 1* (1999).

[27] Eudailey, K. W., Yi, S. Y., Mongero, L. B., Wagener, G., Guarrera, J. V., and George, I. Trans-diaphragmatic left ventricular venting during peripheral venous-arterial extracorporeal membrane oxygenation. *Perfusion 30*, 8 (2015), 701–703.

[28] Fernandez de Canete, J., Luque, J., Barbancho, J., and Munoz, V. Modelling of long-term and short-term mechanisms of arterial pressure control in the cardiovascular system: an object-oriented approach. *Comput. Biol. Med. 47* (Apr. 2014), 104–112.

[29] Fiedler, A. G., Dalia, A., Axtell, A. L., Ortoleva, J., Thomas, S. M., Roy, N., Villavicencio, M. A., D'Alessandro, D. A., and Cudemus, G. Impella placement guided by echocardiography can be used as a strategy to unload the left ventricle during peripheral venoarterial extracorporeal membrane oxygenation. *Journal of cardiothoracic and vascular anesthesia 32*, 6 (2018), 2585–2591.

[30] Fisher, A. R., Baker, M., Buffin, M., Campbell, P., Hansbro, S., Kennington, S., Lilley, A., and Whitehorne, M. Normal and abnormal trans-oxygenator pressure gradients during cardiopulmonary bypass. *Perfusion 18*, 1 (Mar. 2003), 25–30.

[31] Formica, F., and Paolini, G. Veno-arterial extracorporeal membrane oxygenation for refractory cardiogenic shock and cardiac arrest. In *Principles and Practice of Cardiothoracic Surgery*. InTech, 2013.

[32] Fouilloux, V., Lebrun, L., Macé, L., and Kreitmann, B. Extracorporeal membranous oxygenation and left atrial decompression: a fast and minimally invasive approach. *Ann. Thorac. Surg. 91*, 6 (June 2011), 1996–1997.

[33] Fritzson, P. *Principles of Object Oriented Modeling and Simulation with Modelica 3.3: A Cyber-Physical Approach*. Dec. 2014.

[34] Fuhrman, B. P., Hernan, L. J., Rotta, A. T., Heard, C. M., and Rosenkranz, E. R. Pathophysiology of cardiac extracorporeal membrane oxygenation. *Artificial organs 23*, 11 (1999), 966–969.

[35] Fumagalli, R., Bombino, M., Borelli, M., Rossi, F., Colombo, V., Osculati, G., Ferrazzi, P., Pesenti, A., and Gattinoni, L. Percutaneous bridge to

heart transplantation by venoarterial ECMO and transaortic left ventricular venting. *Int. J. Artif. Organs 27*, 5 (May 2004), 410–413.

[36] Gaudard, P., Mourad, M., Eliet, J., Zeroual, N., Culas, G., Rouvière, P., Albat, B., and Colson, P. Management and outcome of patients supported with impella 5.0 for refractory cardiogenic shock. *Critical Care 19*, 1 (2015), 363.

[37] Grasselli, G., Pesenti, A., Marcolin, R., Patroniti, N., Isgró, S., Taglibue, P., Lucchini, A., and Fumagalli, R. Percutaneous vascular cannulation for extracorporeal life support (ECLS): a modified technique. *Int. J. Artif. Organs 33*, 8 (Aug. 2010), 553–557.

[38] Hacking, D. F., Best, D., d'Udekem, Y., Brizard, C. P., Konstantinov, I. E., Millar, J., and Butt, W. Elective decompression of the left ventricle in pediatric patients may reduce the duration of venoarterial extracorporeal membrane oxygenation. *Artificial organs 39*, 4 (2015), 319–326.

[39] Higgs, Z., Macafee, D., Braithwaite, B., and Maxwell-Armstrong, C. The seldinger technique: 50 years on. *The Lancet 366*, 9494 (2005), 1407–1409.

[40] Hirschl, R. B., Heiss, K. F., and Bartlett, R. H. Severe myocardial dysfunction during extracorporeal membrane oxygenation. *Journal of pediatric surgery 27*, 1 (1992), 48–53.

[41] Hochman, J. S., and E Magnus Ohman, M. *Cardiogenic shock*. John Wiley & Sons, 2009.

[42] Hong, T. H., Byun, J. H., Lee, H. M., Kim, Y. H., Kang, G.-H., Oh, J. H., Hwang, S. W., Kim, H. Y., and Park, J. H. Initial experience of transaortic catheter venting in patients with venoarterial extracorporeal membrane oxygenation for cardiogenic shock. *Asaio Journal 62*, 2 (2016), 117–122.

[43] Huang, C.-T., Tsai, Y.-J., Tsai, P.-R., and Ko, W.-J. Extracorporeal membrane oxygenation resuscitation in adult patients with refractory septic shock. *J. Thorac. Cardiovasc. Surg. 146*, 5 (Nov. 2013), 1041–1046.

[44] Jayaraman, A. L., Cormican, D., Shah, P., and Ramakrishna, H. Cannulation strategies in adult veno-arterial and veno-venous extracorporeal membrane oxygenation: Techniques, limitations, and special considerations. *Annals of cardiac anaesthesia 20*, Suppl 1 (2017), S11.

[45] Jegger, D., Corno, A. F., Mucciolo, A., Mucciolo, G., Boone, Y., Horisberger, J., Seigneul, I., Jachertz, M., and von Segesser, L. K. A prototype paediatric venous cannula with shape change in situ. *Perfusion 18*, 1 (Mar. 2003), 61–65.

[46] Ježek, F., Kroček, T., Matejak, M., and Kofránek, J. Inovace výuky modelování a simulace na FEL čvut. *Sborník Příspěvků MEDSOFT* (2012).

[47] Karr, S. S., Martin, G. R., and Short, B. L. Cardiac performance in infants referred for extracorporeal membrane oxygenation. *The Journal of pediatrics 118*, 3 (1991), 437–442.

[48] Kimball, T. R., Daniels, S. R., Weiss, R. G., Meyer, R. A., Hannon, D. W., Ryckman, F. C., Tian, J., Shukia, R., and Schwartz, D. C. Changes in cardiac function during extracorporeal membrane oxygenation for persistent pulmonary hypertension in the newborn infant. *The Journal of pediatrics 118*, 3 (1991), 431–436.

[49] Ko, M., dos Santos, P. R., Machuca, T. N., Marseu, K., Waddell, T. K., Keshavjee, S., and Cypel, M. Use of single-cannula venous-venous extracorporeal life support in the management of life-threatening airway obstruction. *Ann. Thorac. Surg. 99*, 3 (Mar. 2015), e63–5.

[50] Koeckert, M. S., Jorde, U. P., Naka, Y., Moses, J. W., and Takayama, H. Impella LP 2.5 for left ventricular unloading during venoarterial extracorporeal membrane oxygenation support. *J. Card. Surg. 26*, 6 (Nov. 2011), 666–668.

[51] Kohler, K., Valchanov, K., Nias, G., and Vuylsteke, A. Ecmo cannula review. *Perfusion 28*, 2 (2013), 114–124.

[52] Kotani, Y., Chetan, D., Rodrigues, W., Sivarajan, V. B., Gruenwald, C., Guerguerian, A.-M., Van Arsdell, G. S., and Honjo, O. Left atrial decompression during venoarterial extracorporeal membrane oxygenation for left ventricular failure in children: current strategy and clinical outcomes. *Artif. Organs 37*, 1 (Jan. 2013), 29–36.

[53] Kulhánek, T., Tribula, M., Kofránek, J., and Mateják, M. Simple models of the cardiovascular system for educational and research purposes. *MEFANET Journal 2*, 2 (Nov. 2014), 56–63.

[54] Lacko, S., Kittnar, O., Mlček, M., Hála, P., Popková, M., Janák, D., Hrachovina, M., Kudlička, J., Hrachovina, V., and Ošt'ádal, P. Severe acute heart failure-experimental model with very low mortality. *Physiological research 67*, 4 (2018), 555–562.

[55] Le Guen, M., Nicolas-Robin, A., Carreira, S., Raux, M., Leprince, P., Riou, B., and Langeron, O. Extracorporeal life support following out-of-hospital refractory cardiac arrest. *Critical care 15*, 1 (2011), R29.

[56] Léger, P.-L., Guilbert, J., Isambert, S., Le Saché, N., Hallalel, F., Amblard, A., Chevalier, J.-Y., and Renolleau, S. Pediatric single-lumen cannula venovenous extracorporeal membrane oxygenation: a french center experience. *Artif. Organs 37*, 1 (Jan. 2013), 57–65.

[57] Lemaitre, F., Hasni, N., Leprince, P., Corvol, E., Belhabib, G., Fillâtre, P., Luyt, C.-E., Leven, C., Farinotti, R., Fernandez, C., and Combes, A. Propofol, midazolam, vancomycin and cyclosporine therapeutic drug monitoring in extracorporeal membrane oxygenation circuits primed with whole human blood. *Crit. Care 19* (Feb. 2015), 40.

[58] Lequier, L., Horton, S. B., McMullan, D. M., and Bartlett, R. H. Extracorporeal membrane oxygenation circuitry. *Pediatr. Crit. Care Med. 14*, 5 Suppl 1 (June 2013), S7–12.

[59] Leslie, D. C., Waterhouse, A., Berthet, J. B., Valentin, T. M., Watters, A. L., Jain, A., Kim, P., Hatton, B. D., Nedder, A., Donovan, K., Super, E. H., Howell, C., Johnson, C. P., Vu, T. L., Bolgen, D. E., Rifai, S., Hansen, A. R., Aizenberg, M., Super, M., Aizenberg, J., and Ingber, D. E. A bioinspired omniphobic surface coating on medical devices prevents thrombosis and biofouling. *Nat. Biotechnol. 32*, 11 (Nov. 2014), 1134–1140.

[60] Lich, B. V., and Perfusion.com, Incorporated. *The Manual of Clinical Perfusion: Second Edition Updated*. Perfusion.com, Incorporated, 2004.

[61] Lim, H. S., Howell, N., and Ranasinghe, A. Extracorporeal life support: physiological concepts and clinical outcomes. *Journal of cardiac failure 23*, 2 (2017), 181–196.

[62] Ma, P., Zhang, Z., Song, T., Yang, Y., Meng, G., Zhao, J., Wang, C., Gu, K., Peng, J., Jiang, B., et al. Combining ecmo with iabp for the treatment of critically ill adult heart failure patients. *Heart, Lung and Circulation 23*, 4 (2014), 363–368.

[63] Madershahian, N., Nagib, R., Wippermann, J., Strauch, J., and Wahlers, T. A simple technique of distal limb perfusion during prolonged femoro-femoral cannulation. *J. Card. Surg. 21*, 2 (Mar. 2006), 168–169.

[64] Maggio, P., Hemmila, M., Haft, J., and Bartlett, R. Extracorporeal life support for massive pulmonary embolism. *J. Trauma 62*, 3 (Mar. 2007), 570–576.

[65] Maqued. *HLS Cannulae*, Mar. 2015.

[66] Maquet. *Avalon Elite® Bi-Caval Dual Lumen Catheter*, May 2015.

[67] Maquet. *QUADROX-i Adult and Small Adult*, Mar. 2015.

[68] Massetti, M., Gaudino, M., and Crea, F. How to transform peripheral extracorporeal membrane oxygenation in the simplest mid-term paracorporeal ventricular assist device, 2013.

[69] Mateják, M., Kulhánek, T., Šilar, J., Privitzer, P., and others. Physiolibrary-Modelica library for physiology. *Proceedings of the 10 th* (2014).

[70] Mateják, M., and Others. Physiology in modelica. *Mefanet Journal 2*, 1 (2014), 10–14.

[71] Mathur, M., Hira, R. S., Smith, B. M., Lombardi, W. L., and McCabe, J. M. Fully percutaneous technique for transaxillary implantation of the impella cp. *JACC: Cardiovascular Interventions 9*, 11 (2016), 1196–1198.

[72] Matsui, Y., Shimura, S., Suto, Y., Fukase, S., Tanaka, A., and Sasaki, S. A novel femoral arterial cannula to prevent limb ischemia during cardiopulmonary support: preliminary report of experimental and clinical experiences. *Artif. Organs 30*, 7 (July 2006), 557–560.

[73] Meani, P., Gelsomino, S., Natour, E., Johnson, D. M., Rocca, H.-P. B. L., Pappalardo, F., Bidar, E., Makhoul, M., Raffa, G., Heuts, S., et al. Modalities and effects of left ventricle unloading on extracorporeal life support: a review of the current literature. *European journal of heart failure 19* (2017), 84–91.

[74] Medtronic. Extracorporeal circuit. https://www.medtronic.com/us-en/healthcare-professionals/products/cardiovascular/cannulae/adult-extracorporeal-circuit.html. Accessed: 2019-1-6.

[75] Medtronic. *Bio-Medicus Cannulae Family*, 2011.

[76] Menon, P. G., Antaki, J. F., Undar, A., and Pekkan, K. Aortic outflow cannula tip design and orientation impacts cerebral perfusion during pediatric cardiopulmonary bypass procedures. *Ann. Biomed. Eng. 41*, 12 (Dec. 2013), 2588–2602.

[77] Munakata, R., Yamamoto, T., Hosokawa, Y., Tokita, Y., Akutsu, K., Sato, N., Murata, S., Tajima, H., Mizuno, K., and Tanaka, K. Massive pulmonary embolism requiring extracorporeal life support treated with catheter-based interventions. *Int. Heart J. 53*, 6 (2012), 370–374.

[78] Napp, L., Kühn, C., and Bauersachs, J. Ecmo in cardiac arrest and cardiogenic shock. *Herz 42*, 1 (2017), 27–44.

[79] Napp, L. C., and Bauersachs, J. Triple cannulation ECMO. In *Extracorporeal Membrane Oxygenation: Advances in Therapy*, M. S. Firstenberg, Ed. InTech, Sept. 2016.

[80] Napp, L. C., Kühn, C., Hoeper, M. M., Vogel-Claussen, J., Haverich, A., Schäfer, A., and Bauersachs, J. Cannulation strategies for percutaneous extracorporeal membrane oxygenation in adults. *Clin. Res. Cardiol. 105*, 4 (Apr. 2016), 283–296.

[81] Narain, S., Paparcuri, G., Fuhrman, T. M., Silverman, R. B., and Peruzzi, W. T. Novel combination of impella and extra corporeal membrane oxygenation as a bridge to full recovery in fulminant myocarditis. *Case Rep Crit Care 2012* (July 2012), 459296.

[82] Nekic, P., and SWSLHD, C. L. I. Extra corporeal oxygenation (ecmo) learning package. *Liverpool Hospital* (2016).

[83] Nelson, D., Mohammed, A., and Klein, E. Impella 5.0 as a bridge to clinical decision making. *The Journal of Heart and Lung Transplantation 38*, 4 (2019), S437.

[84] Origen. *Reinforced Dual Lumen Catheters*, 2017.

[85] Ošt'ádal, P., and Bělohlávek, J. *ECMO: extrakorporální membránová oxygenace: manuál pro použití u dospělých*. Maxdorf, 2013.

[86] Ostadal, P., Mlcek, M., Gorhan, H., Simundic, I., Strunina, S., Hrachovina, M., Krüger, A., Vondrakova, D., Janotka, M., Hala, P., et al. Electrocardiogram-synchronized pulsatile extracorporeal life support preserves left ventricular function and coronary flow in a porcine model of cardiogenic shock. *PloS one 13*, 4 (2018), e0196321.

[87] Ostadal, P., Mlcek, M., Kruger, A., Hala, P., Lacko, S., Mates, M., Vondrakova, D., Svoboda, T., Hrachovina, M., Janotka, M., Psotova, H., Strunina, S., Kittnar, O., and Neuzil, P. Increasing venoarterial extracorporeal membrane oxygenation flow negatively affects left ventricular performance in a porcine model of cardiogenic shock. *J. Transl. Med. 13* (Aug. 2015), 266.

[88] Ostadal, P., Mlcek, M., Strunina, S., Hrachovina, M., Kruger, A., Vondrakova, D., Janotka, M., Hala, P., Kittnar, O., and Neuzil, P. Novel porcine model of acute severe cardiogenic shock developed by upper-body hypoxia. *Physiological research 65*, 4 (2016), 711.

[89] Pappalardo, F., Schulte, C., Pieri, M., Schrage, B., Contri, R., Soeffker, G., Greco, T., Lembo, R., Müllerleile, K., Colombo, A., et al. Concomitant implantation of impella® on top of veno-arterial extracorporeal mem-

brane oxygenation may improve survival of patients with cardiogenic shock. *European journal of heart failure 19*, 3 (2017), 404–412.

[90] Park, J. Y. The need of slanted side holes for venous cannulae. *Computational and mathematical methods in medicine 2012* (2012).

[91] Park, T. K., Yang, J. H., Choi, S.-H., Song, Y. B., Hahn, J.-Y., Choi, J.-H., Sung, K., Lee, Y. T., and Gwon, H.-C. Clinical impact of intra-aortic balloon pump during extracorporeal life support in patients with acute myocardial infarction complicated by cardiogenic shock. *BMC Anesthesiol. 14* (Apr. 2014), 27.

[92] Petroni, T., Harrois, A., Amour, J., Lebreton, G., Brechot, N., Tanaka, S., Luyt, C.-E., Trouillet, J.-L., Chastre, J., Leprince, P., Duranteau, J., and Combes, A. Intra-aortic balloon pump effects on macrocirculation and microcirculation in cardiogenic shock patients supported by venoarterial extracorporeal membrane oxygenation*. *Crit. Care Med. 42*, 9 (Sept. 2014), 2075–2082.

[93] Psotova, H., Ostadal, P., Mlcek, M., Kruger, A., Janotka, M., Vondrakova, D., Svoboda, T., Hrachovina, M., Taborsky, L., Dudkova, V., et al. Ischemic postconditioning and nitric oxide administration failed to confer protective effects in a porcine model of extracorporeal cardiopulmonary resuscitation. *Artificial organs 40*, 4 (2016), 353–359.

[94] Pyles, L. A., Gustafson, R. A., Fortney, J., and Einzig, S. Extracorporeal membrane oxygenation induced cardiac dysfunction in newborn lambs. *Journal of cardiovascular translational research 3*, 6 (2010), 625–634.

[95] Qiu, F., Clark, J., Kunselman, A., Ündar, A., and Myers, J. Hemodynamic evaluation of arterial and venous cannulae performance in a simulated neonatal extracorporeal life support circuit. *Perfusion 26*, 4 (2011), 276–283.

[96] Reickert, C. A., Schreiner, R. J., Bartlett, R. H., and Hirschl, R. B. Percutaneous access for venovenous extracorporeal life support in neonates. *Journal of pediatric surgery 33*, 2 (1998), 365–369.

[97] Rizkallah, J., Shen, S., Tischenko, A., Zieroth, S., Freed, D. H., and Khadem, A. Successful ablation of idiopathic left ventricular tachycardia in an adult patient during extracorporeal membrane oxygenation treatment. *Can. J. Cardiol. 29*, 12 (Dec. 2013), 1741.e17–9.

[98] Saito, N., Motoyama, S., and Sawamoto, J. Effects of new polymer-coated extracorporeal circuits on biocompatibility during cardiopulmonary bypass. *Artif. Organs 24*, 7 (July 2000), 547–554.

[99] Sauren, L. D. C., Reesink, K. D., Selder, J. L., Beghi, C., van der Veen, F. H., and Maessen, J. G. The acute effect of intra-aortic balloon counterpulsation during extracorporeal life support: an experimental study. *Artif. Organs 31*, 1 (Jan. 2007), 31–38.

[100] Schmidt, F., Kuebler, J., Ganter, M., Jack, T., Meschenmoser, L., Sasse, M., Boehne, M., Bertram, H., Beerbaum, P., and Koeditz, H. Minimal invasive lung support via umbilical vein with a double-lumen cannula in a neonatal lamb model: a proof of principle. *Pediatr. Surg. Int. 32*, 1 (Jan. 2016), 75–82.

[101] Schook, L., and Tumbleson, M. *Advances in Swine in Biomedical Research*. No. sv. 1 in Advances in Swine in Biomedical Research. Springer US, 1997.

[102] Schook, L., and Tumbleson, M. *Advances in Swine in Biomedical Research*. No. sv. 2. Springer US, 2013.

[103] Seib, P. M., Faulkner, S. C., Erickson, C. C., Van Devanter, S. H., Harrell, J. E., Fasules, J. W., Frazier, E. A., and Morrow, W. R. Blade

and balloon atrial septostomy for left heart decompression in patients with severe ventricular dysfunction on extracorporeal membrane oxygenation. *Catheter. Cardiovasc. Interv. 46*, 2 (Feb. 1999), 179–186.

[104] Sidebotham, D., Allen, S., McGeorge, A., and Beca, J. Catastrophic left heart distension following initiation of venoarterial extracorporeal membrane oxygenation in a patient with mild aortic regurgitation. *Anaesth. Intensive Care 40*, 3 (May 2012), 568–569.

[105] Silverthorn, D. U., Ober, W. C., Garrison, C. W., Silverthorn, A. C., and Johnson, B. R. *Human physiology: an integrated approach*. Pearson/Benjamin Cummings San Francisco, CA:, 2004.

[106] Soleimani, B., and Pae, W. Management of left ventricular distension during peripheral extracorporeal membrane oxygenation for cardiogenic shock. *Perfusion 27*, 4 (2012), 326–331.

[107] Soleimani, B., and Pae, W. E. Management of left ventricular distension during peripheral extracorporeal membrane oxygenation for cardiogenic shock. *Perfusion 27*, 4 (July 2012), 326–331.

[108] Spector, K. S., and Lawson, W. E. Optimizing safe femoral access during cardiac catheterization. *Catheterization and cardiovascular interventions 53*, 2 (2001), 209–212.

[109] Strunina, S., Hozman, J., and Ostadal, P. Relation between left ventricular unloading during ecmo and drainage catheter size assessed by mathematical modeling. *Acta Polytechnica 57*, 5 (2017), 367–372.

[110] Strunina, S., Hozman, J., and Ostadal, P. Analysis of left ventricular unloading by double lumen arterial cannula during ecmo assessed by mathematical modeling. In *World Congress on Medical Physics and Biomedical Engineering 2018* (2019), vol. 68, Springer, Singapore, pp. 749–753.

[111] Strunina, S., and Ostadal, P. Left ventricle unloading during veno-arterial extracorporeal membrane oxygenation. *Current Research: Cardiology 3*, 1 (2016).

[112] Swartz, M. F., Smith, F., Byrum, C. J., and Alfieris, G. M. Transseptal catheter decompression of the left ventricle during extracorporeal membrane oxygenation. *Pediatr. Cardiol. 33*, 1 (Jan. 2012), 185–187.

[113] Takayama, H., Landes, E., Truby, L., Fujita, K., Kirtane, A. J., Mongero, L., Yuzefpolskaya, M., Colombo, P. C., Jorde, U. P., Kurlansky, P. A., Takeda, K., and Naka, Y. Feasibility of smaller arterial cannulas in venoarterial extracorporeal membrane oxygenation. *J. Thorac. Cardiovasc. Surg. 149*, 5 (May 2015), 1428–1433.

[114] Thiele, H., Zeymer, U., Neumann, F.-J., Ferenc, M., Olbrich, H.-G., Hausleiter, J., Richardt, G., Hennersdorf, M., Empen, K., Fuernau, G., Desch, S., Eitel, I., Hambrecht, R., Fuhrmann, J., Böhm, M., Ebelt, H., Schneider, S., Schuler, G., Werdan, K., and IABP-SHOCK II Trial Investigators. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N. Engl. J. Med. 367*, 14 (Oct. 2012), 1287–1296.

[115] Tiller, M. M. Modelica by example, 2014. *URL: http://book. xogeny. com.*

[116] Uggla, B., and Nilsson, T. K. Whole blood viscosity in plasma cell dyscrasias. *Clin. Biochem. 48*, 3 (Feb. 2015), 122–124.

[117] Vase, H., Christensen, S., Christiansen, A., Therkelsen, C. J., Christiansen, E. H., Eiskjær, H., and Poulsen, S. H. The impella cp device for acute mechanical circulatory support in refractory cardiac arrest. *Resuscitation 112* (2017), 70–74.

[118] Venables, W. N., Smith, D. M., Team, R. D. C., et al. An introduction to r, 2009.

[119] Wang, S., Kunselman, A. R., and Ündar, A. Evaluation of capiox RX25 and quadrox-i adult hollow fiber membrane oxygenators in a simulated cardiopulmonary bypass circuit. *Artif. Organs 40*, 5 (May 2016), E69–78.

[120] Weymann, A., Schmack, B., Sabashnikov, A., Bowles, C. T., Raake, P., Arif, R., Verch, M., Tochtermann, U., Roggenbach, J., Popov, A. F., et al. Central extracorporeal life support with left ventricular decompression for the treatment of refractory cardiogenic shock and lung failure. *Journal of cardiothoracic surgery 9*, 1 (2014), 60.

[121] Wilson, W. C., Grande, C. M., and Hoyt, D. B. *Trauma: critical care*. CRC Press, 2007.

[122] Wu, Z. J., Taskin, M. E., Zhang, T., Fraser, K. H., and Griffith, B. P. Computational model-based design of a wearable artificial pump-lung for cardiopulmonary/respiratory support. *Artificial organs 36*, 4 (2012), 387–399.

[123] Yang, Z., Tu, Q., Maitz, M. F., Zhou, S., Wang, J., and Huang, N. Direct thrombin inhibitor-bivalirudin functionalized plasma polymerized allylamine coating for improved biocompatibility of vascular devices. *Biomaterials 33*, 32 (Nov. 2012), 7959–7971.

Symbols and abbreviations

ΔP Pressure reduction

μ Dynamic viscosity

${}_{P}CO$ Pulmonary cardiac output

${}_{LV}CO$ Left ventricular cardiac output

$ArtD$ Arterial diastolic blood pressure

AV Aortic valve

$BBAS$ Blade and balloon atrial septostomy

$BVLD$ Bivalirudin

CRP Cardiopulmonary resuscitation

CS Cardiogenic shock

$diaPressure$ Diastolic blood pressure

$DLAC$ Double lumen arterial cannula

dP/dt Left ventricular contractility

EBF Extracorporeal blood flow

$ECLS$ Extracorporeal life support

$ECMO$ Extracorporeal membrane oxygenation support

EDP Left ventricular end-diastolic pressure

EDV Left ventricular end-diastolic volume

ESV Left ventricular end-systolic volume

$F_{i_{in}}$ Input flow rate

$F_{i_{out}}$ Output flow rate

F_{ij} Flow rate between compartments i and j

F_{in} Input flow

F_{out} Output flow

HR Heart rate

$IABP$ Intra-Aortic Balloon Pump

$IABP - SHOCK$ Intra-Aortic Balloon Pump in cardiogenic shock

L Length of pipe

LCS Life circulatory support

LV Left ventricle

$LVEF$ Left ventricular ejection fraction

P_i A pressure of compartment i

P_j A pressure of compartment j

P_{in} Input pressure

P_{out} Output pressure

$PAWP$ Pulmonary artery wedge pressure

$PPAam$ Plasma polymerized allylamine

PV Pressure-volume

Q Volumetric flow rate

r Pipe radius

R_{ij} A resistance between compartments i and j

$RecF$ Recirculation fraction

$RecV$ Recirculation minute volume

$ROSC$ Return of spontaneous circulation

SBP Left ventricular systolic blood pressure

SS Stainless steel

SV Left ventricular stroke volume

SvO_2 Venous oxygen saturation

$sysPressure$ Systolic blood pressure

tc Relative time in cardiac cycle

$TD1$ Relative time of start of systole

$TD2$ Relative time of end of systole

TLP Tethered–Liquid Perfluorocarbon

V_i Blood volume

$VA-ECMO$ Veno-arterial extracorporeal membrane oxygenation

$VV-ECMO$ Veno-venous extracorporeal membrane oxygenation

List of Figures

List of Tables

Appendix A: List of author‘s publications

Articles in Impacted Journals

1. Ostadal, P., Mlcek, M., Kruger, A., Hala, P., Lacko, S.,Mates, M., Vondrakova, D., Svoboda, T., Hrachovina, M., Janotka, M., et al. Increasing venoarterial extracorporeal membrane oxygenation flow negatively affects left ventricular performance in a porcine model of cardiogenic shock. Journal of translational medicine 13, 1 (2015), 266. (IF 3.786, Q1, SRJ 2017: 1,56)

2. Ostadal, P., Mlcek, M., Strunina, S., Hrachovina, M.,Kruger, A., Vondrakova, D., Janotka, M., Hala, P., Kit-tnar, O., and Neuzil, P. Novel porcine model of acute severe cardiogenic shock developed by upper-body hypoxia. Physiological research 65, 4 (2016), 711. (Nov. 2016), 711–715. (IF 1.697, Q2, SRJ 2017: 0,57)

3. Psotova, H., Ostadal, P., Mlcek, M., Kruger, A., Jan-otka, M., Vondrakova, D., Svoboda, T., Hrachovina, M.,Taborsky, L., Dudkova, V., et al. Ischemic postconditioning and nitric oxide administration failed to confer protective effects in a porcinemodel of extracorporeal cardiopulmonary resuscitation. Artificial organs 40, 4 (2016), 353–359. (IF 2.111, Q2, SRJ 2017: 0,74)

4. Ostadal, P., Mlcek, M., Gorhan, H., Simundic, I., Strunina,S., Hrachovina, M., Kr uger, A., Vondrakova, D., Janotka,M., Hala, P., et al. Electrocardiogram-synchronized pulsatile extracorporeal life support preserves left ventricular function and coronary flow in a porcine model of cardiogenic shock. PloS One 13, 4 (2018), e0196321. (IF 2,766, Q1, SRJ 2017: 1,16)

5. Strunina, S., Hozman, J., and Ostadal, P. The peripheral cannulas in extracorporeal life support. Biomedical Engineer-ing/Biomedizinische Technik 64, 2 (2018), 127–133. (IF 1.096, SJR 2017: 0.202, SNIP 2017: 0.356)

6. Strunina, S., and Ostadal, P. Left ventricle unloading during veno-arterial extracorporeal membrane oxygenation. Current Research: Cardiology 3, 1 (2016), 98–105. (IF 0.42, Index Copernicus Value: 69.57, Indexed in: CNKI, Open J-Gate)

7. Jezek, F.; Strunina, S.; Carlson, B.E.; Hozman, J. A simulation study of left ventricular decompression using a double lumen arterial cannula prototype during a veno-arterial ECMO. International Journal of Artificial Organs. 2019, ISSN 0391-3988. (in print) (IF 2.111, Q2, SRJ 2017: 0,74)

Articles in Reviewed Journals

8. Strunina, S., Hozman, J., and Ostadal, P. Relation between leftventricular unloading during ECMO and drainage catheter size assessed by mathematical modeling. Acta Polytechnica 57, 5 (2017), 367–372. (Q3, SRJ 2017: 0,21)

Other publications

9. Ostadal, P., Mlcek, M., Strunina, S., Hrachovina, M.,Kruger, A., Vondrakova, D., Janotka, M., Kittnar, O., and Neuzil, P. Synchronized pulsatile extracorporeal life support preserves left ventricular functions in comparison with continuous extracorporeal flow in porcine model of cardiogenic shock. Circulation 132, suppl 3 (2015), A19380.

10. Erdeneochir, E., and Strunina, S. Analysis of blood flow in extracorporeal membrane oxygenation circuit. In International Student Scientific Conference Poster 21(2017), Czech Technical University in Prague, Czech Republic, pp. 1–4.

11. Strunina, S., Hozman, J., and Ostadal, P. Analysis of left ventricular unloading by double lumen arterial cannula during ECMO assessed by mathematical modeling. In World Congress on Medical Physics and Biomedical Engineering 2018 (2019), vol. 68, Springer, Singapore, pp. 749–753. (SRJ 2017: 0,14)

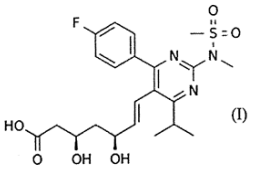
Patent

12. Strunina, S.; Hozman, J.; Ošťádal, P. A cannula containing a base tube with two adjacent longitudinally leading lumens Czech Technical University in Prague, Faculty of Biomedical Engineering. Czech Republic. Patent. CZ 307196. 2018-01-31. Available from: http://isdv.upv.cz/doc/FullFiles/Patents/FullDocuments/307/307196.pdf

Appendix B: The patent document

A61K 47/38 (2006.01)
A61K 47/36 (2006.01)
A61K 47/20 (2006.01)
(21) **2016-539**
(71) Zentiva, k.s., Praha 10 - Dolní Měcholupy, CZ
(72) Prokopová Alena, Praha 10, CZ
Svobodová Jaroslava, Křenice, CZ
Dammer Ondřej, Hostivice, CZ
Mikeš Petr, Praha 9, CZ
(54) **Farmaceutická kompozice obsahující dvě rozdílné účinné látky a způsob její přípravy**
(22) 05.09.2016
(57) Řešení se týká farmaceutické kompozice obsahující účinné látky rosuvastatin vzorce I, chemicky (3*R*,5*S*,6*E*)-7-[4-(4-fluorofenyl)-2-(N-methylmethansulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enová kyselina nebo její farmaceuticky přijatelné soli a ezetimib vzorc II, chemicky (3*R*,4*S*)-1-(4-fluorofenyl)-3-[(3S)-3-(4-fluorofenyl)-3-hydroxypropyl]-4-(4-hydroxyfenyl)azetidin-2-on nebo jeho farmaceuticky přijatelné soli, a také způsob přípravy této farmaceutické kompozice. Hmotností poměr vrstev je 1:2 až 2:1.

(74) Rott, Růžička & Guttmann Patentové, známkové a advokátní kanceláře, Ing. Jana Fuchsová, Vinohradská 37, Praha 2, 12000



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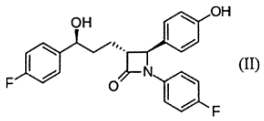
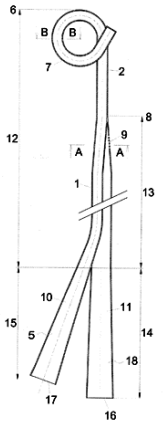


(II)

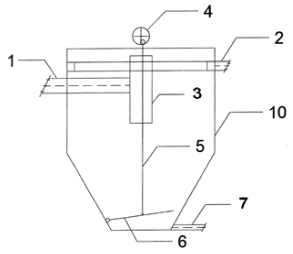
(51) ***A61M 25/00*** (2006.01)
(21) **2016-480**
(71) České vysoké učení technické v Praze, Fakulta biomedicínského inženýrství, Kladno, CZ
(72) Strunina Svitlana Mgr., Praha 2, CZ
Hozman Jiří doc. Ing, Ph.D., Praha 6, Dejvice, CZ
Ošťádal Petr doc. MUDr., Ph.D., Praha 5, CZ
(54) **Kanyla obsahující základní hadičku s dvěma vedle sebe oddělenými podélně vedoucími lumenami**
(22) 08.08.2016
(57) Vynález se týká kanyly obsahující základní hadičku (2) s dvěma vedle sebe oddělenými podélně vedoucími lumenami (3, 4). První lumen (4) pro zavedení do levé srdeční komory má vnitřní průměr 3 až 3,5 mm a je na svém konci opatřen alespoň jedním otvorem (7) a druhý lumen (3) jehož distální konec končí v aortě je na svém konci opatřen alespoň jedním otvorem (9). Celková délka sekce (12) tvořené základní hadičkou (2) a sekcí (13), tvořenou prolínajícími se lumenami (3, 4) je alespoň 100 cm, délka sekce (13) je alespoň 50 cm a délky připojovacích částí (10, 11) mezi jejich distálními a proximálními konci jsou alespoň 5 cm.

(74) Ing. Václav Kratochvíl, Husníkova 2086/22, Praha 13, 15800



(51) ***B01D 21/02*** (2006.01)
B01D 21/28 (2006.01)
B01D 21/18 (2006.01)
C02F 1/52 (2006.01)
(21) **2016-643**
(71) ENVI-PUR s.r.o., Praha 6, CZ
(72) Grau Petr prof. Ing., DrSc., Praha-Újezd, CZ
Drda Milan, Sezimovo Ústí, CZ
(54) **Dosazovák pro zahušťování aktivovaného kalu při čištění odpadních vod**
(22) 13.10.2016
(57) Dosazovák (10) pro zahušťování aktivovaného kalu při čištění odpadních vod v čistírně odpadních vod, tvořený dutým tělesem s jehlancovou nebo kuželovou spodní částí zakončenou rovným dnem, je opatřen pulzátorem, který je tvořený alespoň jednou deskou (6) umístěnou v blízkosti rovného dna dosazováku (10) a pohonem (9) spřaženým s deskou (6) pro kmitavý pohyb desky (6) s dobou trvání kmitu od 1 s do 300 s. Deska, která se cyklicky pohybuje a vnáší do zahuštěného aktivovaného kalu energii, a tím překonává tixotropní vazby v kalu a zlepšuje jeho tekutost.

(74) PatentCentrum Sedlák & Partners s.r.o., Husova 5, České Budějovice, 37001



(51) ***B01D 63/04*** (2006.01)
F28F 21/06 (2006.01)
B01D 69/08 (2006.01)
(21) **2017-226**
(71) Promens a.s., Zlín, Příluky, CZ
(72) Bořuta Jaroslav Ing., CSc., Otrokovice, CZ
Inderka Jan Ing., Zlín, Prštné, CZ
Dědek Hynek Ing., Zlín, Lužkovice, CZ

ČESKÁ REPUBLIKA
ÚŘAD PRŮMYSLOVÉHO VLASTNICTVÍ

PATENTOVÁ LISTINA

Josef Kratochvíl
předseda
Úřadu průmyslového vlastnictví

PATENTOVÝ SPIS

(11) Číslo dokumentu:
307 196
(13) Druh dokumentu: **B6**
(51) Int. Cl.:
A61M 25/00 (2006.01)

(19) ČESKÁ REPUBLIKA

ÚŘAD PRŮMYSLOVÉHO VLASTNICTVÍ

(21) Číslo přihlášky: **2016-480**
(22) Přihlášeno: **08.08.2016**
(40) Zveřejněno: **14.03.2018**
(Věstník č. 11/2018)
(47) Uděleno: **31.01.2018**
(24) Oznámení o udělení ve věstníku: **14.03.2018**
(Věstník č. 11/2018)

(56) Relevantní dokumenty:
Strunina S., et al: Curr Res Cardiol (2016), 3, 5 – 8.
WO 2016/054 543 A1.

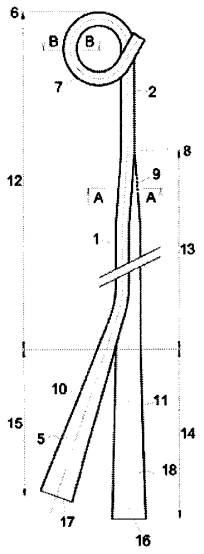
(73) Majitel patentu:
České vysoké učení technické v Praze, Fakulta biomedicínského inženýrství, Kladno, CZ

(72) Původce:
Mgr. Svitlana Strunina, Praha 2, CZ
doc. Ing Jiří Hozman, Ph.D., Praha 6, Dejvice, CZ
doc. MUDr. Petr Ošťádal, Ph.D., Praha 5, CZ

(74) Zástupce:
Ing. Václav Kratochvíl, Husníkova 2086/22, 158 00 Praha 13

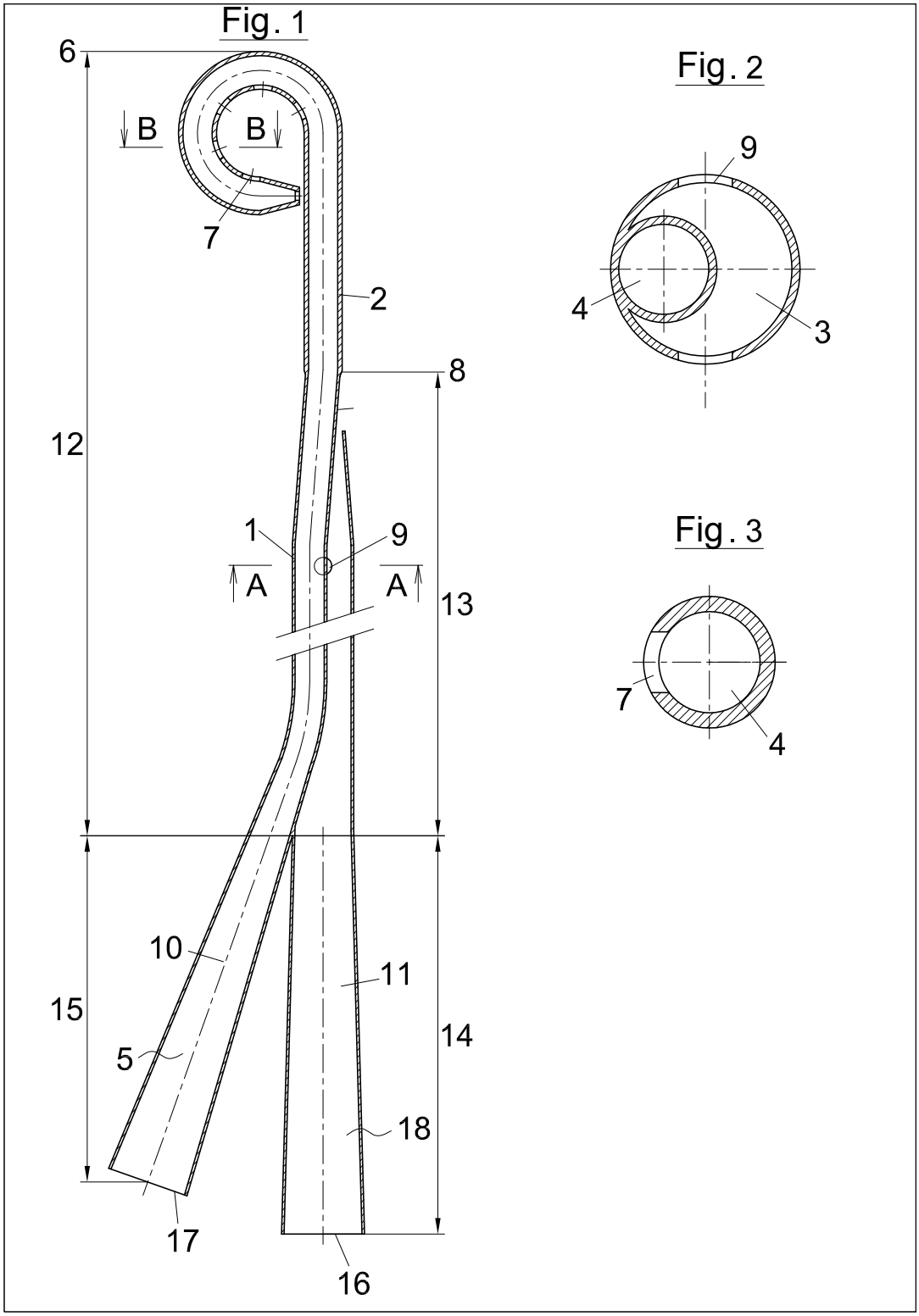
(54) Název vynálezu:
Kanyla obsahující základní hadičku s dvěma vedle sebe oddělenými podélně vedoucími lumenami

(57) Anotace:
Vynález se týká kanyly obsahující základní hadičku (2) s dvěma vedle sebe oddělenými podélně vedoucími lumenami (3, 4). První lumen (4) pro zavedení do levé srdeční komory má vnitřní průměr 3 až 3,5 mm a je na svém konci opatřen alespoň jedním otvorem (7) a druhý lumen (3), jehož distální konec končí v aortě je na svém konci opatřen alespoň jedním otvorem (9). Celková délka sekce (12) tvořené základní hadičkou (2) a sekcí (13), tvořenou prolínajícími se lumenami (3, 4) je alespoň 100 cm, délka sekce (13) je alespoň 50 cm a délky připojovacích částí (10, 11) mezi jejich distálními a proximálními konci jsou alespoň 5 cm.

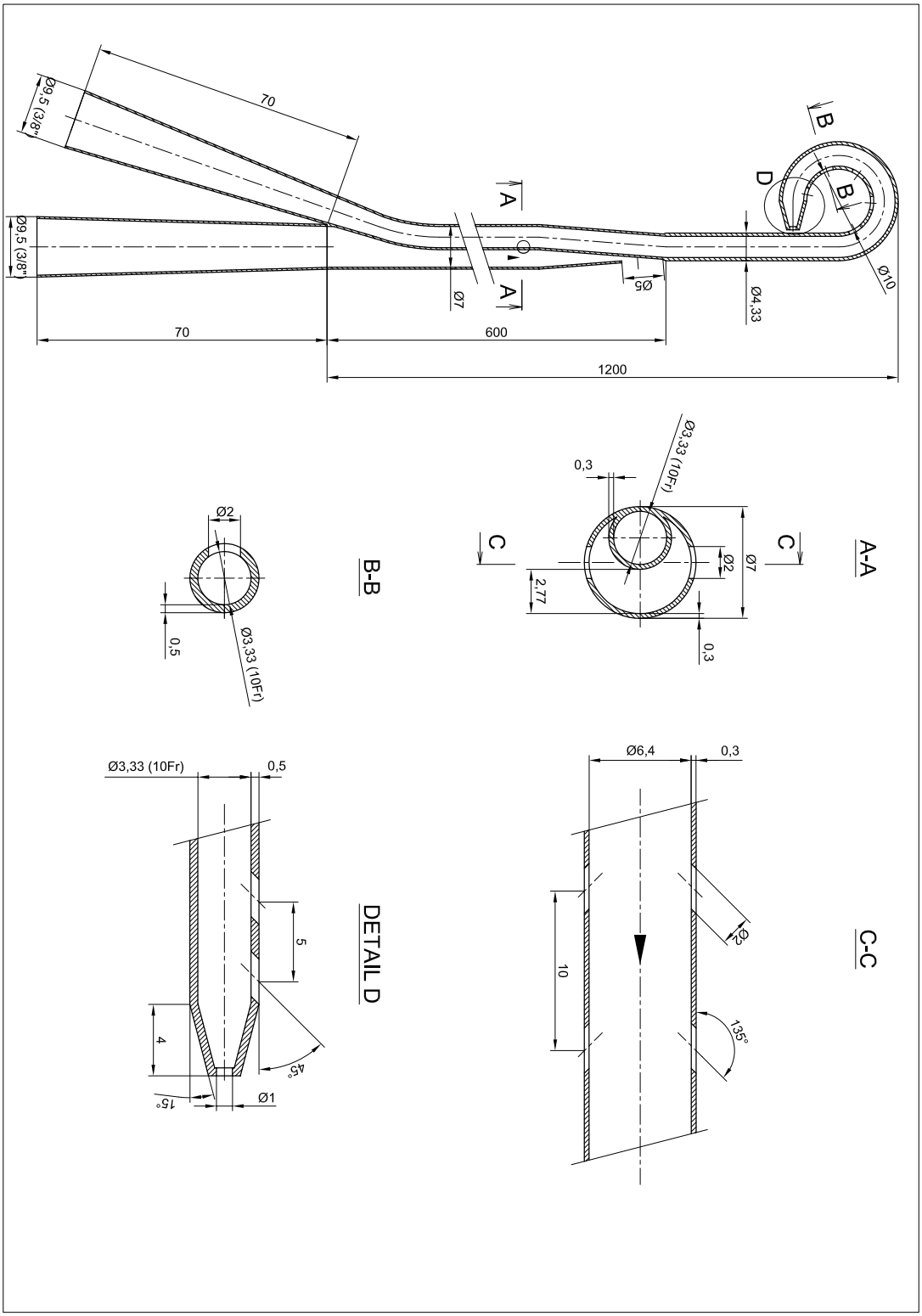


CZ 307196 B6

Appendix C: Description of the preferred embodiment



Appendix D: Manufacturing drawings of double lumen arterial cannula



Appendix E: Modelica code of the model

The model code is on the CD attached to the doctoral thesis.

Appendix F: Simulation results of withdrawal blood value through DLAC drainage lumen, for single cardiac cycle, with applying from 18 Fr to 29 Fr venous cannula sizes

Table 6: The results of simulation with applying from 18 Fr to 29 Fr venous cannula sizes for 5 Fr DLAC drainage lumen

ECMO venous cannula size [Fr]	Extracorporeal blood flow				
	1 L/min	2 L/min	3 L/min	4 L/min	5 L/min
	Withdrawn blood volume during single cardiac cycle [ml]				
18	0.245	0.310	0.373	0.436	0.496
19	0.239	0.299	0.354	0.410	0.462
20	0.235	0.289	0.340	0.389	0.435
21	0.232	0.282	0.328	0.373	0.414
22	0.229	0.277	0.320	0.361	0.398
23	0.227	0.272	0.312	0.351	0.385
24	0.225	0.269	0.307	0.343	0.375
25	0.224	0.266	0.302	0.337	0.366
26	0.223	0.263	0.298	0.331	0.359
27	0.222	0.261	0.295	0.327	0.354
28	0.221	0.260	0.293	0.323	0.349
29	0.220	0.258	0.290	0.320	0.345

Table 7: The results of simulation with applying from 18 Fr to 29 Fr venous cannula sizes for 6 Fr double lumen arterial cannula drainage lumen

ECMO venous cannula size [Fr]	Extracorporeal blood flow				
	1 L/min	2 L/min	3 L/min	4 L/min	5 L/min
	Withdrawn blood volume during single cardiac cycle [ml]				
18	0.503	0.637	0.766	0.895	1.017
19	0.492	0.613	0.728	0.842	0.948
20	0.483	0.595	0.698	0.799	0.893
21	0.476	0.580	0.675	0.768	0.852
22	0.471	0.569	0.657	0.742	0.819
23	0.467	0.560	0.642	0.722	0.792
24	0.463	0.553	0.631	0.705	0.771
25	0.461	0.547	0.621	0.692	0.754
26	0.458	0.542	0.613	0.681	0.739
27	0.457	0.538	0.607	0.672	0.728
28	0.455	0.535	0.602	0.665	0.718
29	0.454	0.532	0.597	0.659	0.710

Table 8: The results of simulation with applying from 18 Fr to 29 Fr venous cannula sizes for 7 Fr double lumen arterial cannula drainage lumen

ECMO venous cannula size [Fr]	Extracorporeal blood flow				
	1 L/min	2 L/min	3 L/min	4 L/min	5 L/min
	Withdrawn blood volume during single cardiac cycle [ml]				
18	0.922	1.168	1.404	1.641	1.866
19	0.903	1.126	1.336	1.545	1.740
20	0.887	1.092	1.282	1.468	1.640
21	0.876	1.067	1.241	1.411	1.565
22	0.866	1.047	1.208	1.365	1.505
23	0.859	1.030	1.181	1.327	1.456
24	0.853	1.017	1.161	1.298	1.418
25	0.848	1.007	1.144	1.274	1.387
26	0.844	0.998	1.129	1.254	1.361
27	0.841	0.991	1.118	1.238	1.339
28	0.838	0.985	1.108	1.224	1.322
29	0.836	0.980	1.100	1.213	1.307

Table 9: The results of simulation with applying from 18 Fr to 29 Fr venous cannula sizes for 8 Fr double lumen arterial cannula drainage lumen

ECMO venous cannula size [Fr]	Extracorporeal blood flow				
	1 L/min	2 L/min	3 L/min	4 L/min	5 L/min
	Withdrawn blood volume during single cardiac cycle [ml]				
18	1.578	2	2.404	2.81	3.194
19	1.547	1.930	2.290	2.648	2.983
20	1.523	1.875	2.199	2.520	2.815
21	1.504	1.833	2.131	2.423	2.688
22	1.489	1.799	2.076	2.346	2.587
23	1.477	1.772	2.032	2.283	2.504
24	1.468	1.750	1.997	2.233	2.440
25	1.460	1.733	1.968	2.193	2.387
26	1.453	1.718	1.944	2.159	2.342
27	1.448	1.706	1.925	2.131	2.307
28	1.444	1.696	1.909	2.109	2.277
29	1.440	1.688	1.895	2.089	2.251

Table 10: The results of simulation with applying from 18 Fr to 29 Fr venous cannula sizes for 9 Fr double lumen arterial cannula drainage lumen

ECMO venous cannula size [Fr]	Extracorporeal blood flow				
	1 L/min	2 L/min	3 L/min	4 L/min	5 L/min
	Withdrawn blood volume during single cardiac cycle [ml]				
18	2.490	3.155	3.791	4.432	5.038
19	2.446	3.051	3.619	4.186	4.714
20	2.410	2.968	3.482	3.989	4.456
21	2.384	2.905	3.377	3.840	4.260
22	2.363	2.854	3.294	3.722	4.104
23	2.345	2.813	3.226	3.624	3.976
24	2.332	2.781	3.172	3.547	3.876
25	2.330	2.754	3.128	3.485	3.794
26	2.311	2.732	3.092	3.432	3.724
27	2.303	2.714	3.062	3.390	3.669
28	2.297	2.699	3.037	3.355	3.623
29	2.292	2.686	3.016	3.325	3.583

Appendix G: Percentage of LV unloading by DLAC with applying from 18 Fr to 29 Fr venous cannula sizes, assessed by mathematical modeling

Table 11: Percentage of left ventricular unloading by 5 Fr double lumen arterial cannula drainage lumen, with applying from 18 Fr to 29 Fr venous cannula sizes

ECMO venous cannula size [Fr]	Extracorporeal blood flow			
	2 L/min	3 L/min	4 L/min	5 L/min
	LV unloading [%]			
18	5	4	3	3
19	5	4	3	2
20	5	3	3	2
21	5	3	3	2
22	5	3	3	2
23	5	3	3	2
24	4	3	2	2
25	4	3	2	2
26	4	3	2	2
27	4	3	2	2
28	4	3	2	2
29	4	3	2	2

Table 12: Percentage of left ventricular unloading by 6 Fr double lumen arterial cannula drainage lumen, with applying from 18 Fr to 29 Fr venous cannula sizes

ECMO venous cannula size [Fr]	Extracorporeal blood flow			
	2 L/min	3 L/min	4 L/min	5 L/min
	LV unloading [%]			
18	11	8	6	5
19	10	7	6	5
20	10	7	6	5
21	10	7	5	4
22	9	7	5	4
23	9	6	5	4
24	9	6	5	4
25	9	6	5	4
26	9	6	5	4
27	9	6	5	4
28	9	6	5	4
29	9	6	5	4

Table 13: Percentage of left ventricular unloading by 7 Fr double lumen arterial cannula drainage lumen, with applying from 18 Fr to 29 Fr venous cannula sizes

ECMO venous cannula size [Fr]	Extracorporeal blood flow			
	2 L/min	3 L/min	4 L/min	5 L/min
	LV unloading [%]			
18	19	14	12	10
19	19	13	11	9
20	18	13	10	9
21	18	12	10	8
22	17	12	10	8
23	17	12	9	8
24	17	12	9	7
25	17	11	9	7
26	17	11	9	7
27	17	11	9	7
28	16	11	9	7
29	16	11	9	7

Table 14: Percentage of left ventricular unloading by 8 Fr double lumen arterial cannula drainage lumen, with applying from 18 Fr to 29 Fr venous cannula sizes

ECMO venous cannula size [Fr]	Extracorporeal blood flow			
	2 L/min	3 L/min	4 L/min	5 L/min
	LV unloading [%]			
18	33	24	20	17
19	32	23	19	16
20	31	22	18	15
21	31	21	17	14
22	30	21	17	14
23	30	20	16	13
24	29	20	16	13
25	29	20	16	13
26	29	19	15	12
27	28	19	15	12
28	28	19	15	12
29	28	19	15	12

Table 15: Percentage of left ventricular unloading by 9 Fr double lumen arterial cannula drainage lumen, with applying from 18 Fr to 29 Fr venous cannula sizes

ECMO venous cannula size [Fr]	Extracorporeal blood flow			
	2 L/min	3 L/min	4 L/min	5 L/min
	LV unloading [%]			
18	53	38	32	27
19	51	36	30	25
20	49	35	28	23
21	48	34	27	22
22	48	33	27	22
23	47	32	26	21
24	46	32	25	20
25	46	31	25	20
26	46	31	25	20
27	45	31	24	19
28	45	30	24	19
29	45	30	24	19

Table 16: Percentage of left ventricular unloading by 10 Fr double lumen arterial cannula drainage lumen, with applying from 18 Fr to 29 Fr venous cannula sizes

ECMO venous cannula size [Fr]	Extracorporeal blood flow			
	2 L/min	3 L/min	4 L/min	5 L/min
	LV unloading [%]			
18	79	57	47	40
19	76	54	45	37
20	74	52	43	35
21	73	51	41	34
22	72	50	40	33
23	71	49	39	32
24	70	48	38	31
25	69	47	38	30
26	69	47	37	30
27	68	46	37	29
28	68	46	36	29
29	68	46	36	29